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CONTENTS OF PREVIOUS NUMBER

JUNE 1947. NUMBER 6

Kernicterus: A Follow-Up Study of Thirty-Five Erythroblastotic Infants. Ralph Stiller, M.D., New York.

Management of Whooping Cough with Special Reference to Infants. Jerome L. Kobb, M.D., and Alfred E. Fischer, M.D., New York.

Familial Hypoplastic Anemia of Childhood: Report of Eight Cases in Two Families with Beneficial Effect of Splenectomy in One Case. Solomon Katzu, M.D., and William Dameshek, M.D., Boston.

Case Reports:
Cardiac Complications in Salmonella Infections. Bernard Harold Shulman, M.D., Brooklyn.

Progress in Pediatrics:
Panel on Prematurity:
Introduction to the Problem of Prematurity. Samuel Z. Levine, M.D., New York.
Prevention and Control of Infections. Julius H. Hess, M.D., Chicago.
Management of Emergencies. Stewart M. Clifford, M.D., Brookline, Mass.
Feeding of Premature Infants. Harry H. Gordon, M.D., Denver.
Discussion.

Abstracts from Current Literature.

News and Comment.

Book Reviews.

Directory of Pediatric Societies.

General Index.

American Journal of Diseases of Children

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CEREBRAL DAMAGE IN INFANTS AND IN CHILDREN

Some Observations on Its Causes and the Possibilities of Its Prevention

HAROLD K. FABER, M.D.
SAN FRANCISCO

THE SUBJECT of my address was chosen with misgivings because so much has already been written about it and I can contribute little that is really new. In extenuation I can only plead that a great deal yet remains to be learned about the subject and that even a minor exploration in a field of major importance might discover something of interest. I venture to discuss today certain aspects of the distressing problem that plagues every pediatrician so often, that of the children with damaged brains who come because of mental deficiency, spastic paralysis, epilepsy and certain other neurologic disorders, occurring singly or in various combinations, and I shall limit the discussion to those with cortical atrophy objectively demonstrated by pneumoencephalogram. Whenever one sees such a child one wonders what was the cause of his trouble, when it began and, most of all, whether it might have been prevented, since in only a minority of cases can one offer more than symptomatic relief and in too many one can do nothing at all.

Granting, as Benda asserts, that a considerable proportion of cases of mental deficiency, especially at the moron levels, are due to hereditary defects, a large number remain that must be due to extrinsic causes operating during the gestational period, during birth or later on. In the various discussions of the subject, attention has, I think, been focused too closely on the period of labor and delivery, the causes being lumped under the general heading of injury at birth, to the relative neglect of the preceding and following periods of life. Thus, the observations of Schreiber and of Cole suggest that the most important causative agents are oversedation and improper anesthesia during labor, which, with certain other observations on the damaging effects on the infant of oxytocic posterior pituitary extracts, have placed much of the blame on the obstetrician. Indeed, my own study was prompted by Schreiber's report and by the idea that pediatricians had been thinking etiologically too much in terms of intracranial hemorrhage and too little in terms of anoxia.

Presidential address, American Pediatric Society, Stockbridge, Mass., May 13, 1947.

The collection of case reports began in 1938, and a preliminary report was presented in 1941 before the Michigan State Medical Society. The present one deals with a much larger material, consisting now of 99 cases, all with demonstrated cerebral atrophy, presumably of extrinsic rather than genetic origin. No infants with mongolism have been included. In each case as thorough a history as possible has been taken with a view to eliciting such episodes or other factors as might have

TABLE 1.—*Period During Which Probable Causative or Contributory Event Occurred*

Prenatal only	21
Paranatal only	26
Postnatal only	20
Prenatal and paranatal	16
Other combinations	10
Inadequate history for prenatal and paranatal periods	6
Total	99
Total prenatal episodes	42, or 35%
Total paranatal episodes	48, or 40%
Total postnatal episodes	30, or 25%

been contributory to cerebral injury. These have been grouped according to the period—prenatal, paranatal or postnatal—during which they occurred. My principal object in presenting these observations is to consider causes and prevention and to what extent the pediatrician, as well as the obstetrician, can contribute to the solution.

In the present series there are 99 cases of cerebral atrophy proved by air encephalogram, in all of which the procedure was carried out because of known mental deficiency, spastic paralysis, convulsive state,

TABLE 2.—*Prenatal Factors*

Placental separation (bleeding), including placenta previa	15
Toxemia	10
Oversize infant (3,800 Gm.)	9
Premature rupture of membranes	5
Maternal trauma (falls, automobile accident)	5
Rh incompatibility (erythroblastosis, probable "kernicterus")	4
Premature labor pains	2
Attempted abortion	2
Cardiac decompensation, maternal	2
Infectious diseases, maternal (pneumonia, influenza, sore throat, rheumatic fever, syphilis, rubella) each 1	6

a combination of two or more of these, or, in 4 cases, other neurologic defects. Mental deficiency was present in 74 per cent; spastic paralysis in 43 per cent, and the convulsive state in 48 per cent of the patients. The times at which probable contributory episodes occurred are shown in table 1.

It will be noted that such episodes occurred during more than one period in 26 instances, that the paranatal period shows only a slightly higher incidence than the prenatal and that the postnatal period is represented in a full quarter of the cases.

Table 2 shows the untoward events of various kinds that were recorded for the period of gestation. Placental separation is by far the most frequent and probably occurred not only in the 15 cases with known bleeding but also in some at least of the cases of toxemia, of maternal trauma and of premature labor pains in which bleeding was not recorded. If my data are representative, placental separation is at least a contributory factor in about 20 per cent of the cases under consideration, causing impairment of the supply of oxygen and doubtless other blood-borne necessities to the fetus. The severity and promptness of the injurious effects on the fetal brain of such impairment have been well shown by Clifford in his study of 11 cases of placenta previa. Toxemia of pregnancy is also conspicuous, although the mechanism by which fetal injury is produced cannot be definitely stated: However, massive infarction of the placenta sufficient to cause fetal death has been observed, as well as placental separation, in this maternal disorder. The number of infants weighing 3,800 Gm. or more at birth, 9 per cent of the series, is notable and strongly suggests a special hazard to the very large infant during labor. In 2 cases, the mother had heart disease with recurrent attacks of dyspnea and, in 1 case, cyanosis, both indicative of decompensation, the effect of which on the fetus was presumably one of stagnant anoxia, that is, of a reduced oxygen supply from slowing of the uterine circulation. Of the infectious diseases observed during pregnancy two are of special interest. Pneumonia reduces the oxygen taken into the blood stream from the air, producing so-called anoxic anoxia and, in the pregnant woman, reducing the oxygen supply to the fetus. In this condition, as in cardiac decompensation and in others not represented in the series, such as anemia, carbon monoxide poisoning and methemoglobinemia, the effect on the fetus may be considerably greater than on the mother, since the fetus lives under conditions of reduced oxygen tension which are compensated for under normal conditions by a higher hemoglobin content of the blood and a fuller utilization of available oxygen in the tissues, but he apparently has a small margin of safety and is therefore highly dependent on a continuous and adequate transplacental supply of oxygen. If this is reduced even slightly below the margin of safety for hours or days, anoxic damage is inevitable, and it is to be remembered that of all the body tissues the cells of the brain cortex are most susceptible to anoxia, while those of the brain stem, including the vital centers of the medulla, are somewhat less so. Thus, anoxia of a certain degree will leave the cortex permanently damaged while permitting the fetus to survive. The same principle applies, of course, to postnatal life.

The other noteworthy infectious disease in the series is rubella, in which the virus apparently invades and damages not only the nervous but also other fetal tissues if maternal infection occurs during the first two months of gestation.

The importance of Rh incompatibility in producing permanent cerebral damage is well known, and this disorder was probably present or actually proved in 4 of the patients. The frequency of this type of injury in relation to all cases of erythroblastosis does not appear to be accurately established, and its exact cause is still open to question. Infants with severe hemolytic anemia due to Rh incompatibility frequently recover without injury to the brain when properly treated. When present, the neurologic damage—to which the misleading name of kernicterus, or nuclear icterus, is generally applied—is not confined to the basal ganglions, which are simply more intensively stained with bilirubin than other parts of the brain, but affects the brain cortex as well, causing some mental deficiency and other symptoms in survivors. In 1 of the 4 cases, cortical atrophy had involved nearly every convolution. The cerebral damage is present at birth and appears not to be dependent at all on the amount of anemia: One infant, not in the present series, died before advanced anemia had occurred. The suggestion of Wiener that the mischief is caused by agglutination thrombi in the brain capillaries appears to be supported by little direct evidence. In a case recently observed in the Stanford University Hospitals no agglutinins were demonstrable in the mother or in the infant, although hemolytic, or blocking, antibodies were present in large amounts. Moreover, examination of sections from a series of 4 cases of so-called kernicterus revealed antemortem thrombi in the basal ganglions or other portions of the brain tissue in only 1. It seems more likely to me that the damage is more often traceable to the profound changes that regularly occur in the placental villi, as described by Hellman and Hertig, consisting of persistence of the Langhans layer, edema and hyperplastic stroma in the chorionic villi, changes that are well adapted to interfere with the exchange of oxygen and perhaps other nutrient substances, leading to anoxic damage to the fetal brain.

A review of the prenatal factors found in this study reveals only a minority that could be considered preventable in some degree. Placental separation, the most frequent contributory event, is certainly only rarely so. Perhaps the future, but not the present, holds some hope of preventing maternal toxemia. In relation to the Rh disease, one preventive measure of some importance, especially to pediatricians, is strict adherence to the rule never to use Rh-positive blood for transfusions in girls not known to be Rh positive. This rule is probably not so universally known and followed as it should be. Another preventive possibility is indicated by the recent work of Page, who suggests that under certain conditions when Rh antibodies, either blocking or agglutinating, do not appear in the maternal blood until relatively late, induction of labor before the fetus has been exposed to them for more than eight to ten weeks may prevent fetal damage. As I have said,

I seriously question whether the giving of transfusions to the newborn infant, no matter how early it is done or how much blood is given, is likely to prevent cerebral damage. Women with cardiac disease which is likely to cause decompensation under the strain of pregnancy should be advised not to have babies, but if they do it would seem to be imperative that every effort be made by the physician to prevent decompensation or, if it should occur, that every effort be made to offset anoxia, which would include the free use of oxygen. The special importance of oxygen to the gravid woman with pneumonia can hardly be overemphasized. As yet no active means of preventing rubella is available. On the other hand, when there is an opportunity, it may be wise to encourage exposure of young girls to this nearly always mild disease.

TABLE 3.—*Paranatal Factors*

Anesthetics		
Nitrous oxide		22
Chloroform		4
Ether		8
Spinal		1
Sedation		
Unspecified "shots"		5
"Pills" and specified barbiturates		5
Sedation, heavy (judged by effect on mother)		6
Induced labor		
Oxytocics (probably "pitocin")		2
Castor oil		1
Quinine		1
Breech presentation		9
Delivery, abnormal		22
Prolonged	7	
Dry	4	
Version	2	
Precipitate	5	
Cesarean	3	
High forceps	1	
Abnormalities of cord		6
Very tight about neck	4	
Prolapse	1	
Very short	1	

The paranatal factors, some of them possibly and others almost certainly injurious to the infant, are shown in table 3. Outstanding is the large number of difficult deliveries, of breech presentations and of abnormalities of the cord, all of which menace the oxygen supply to the infant, and some of which favor intracranial hemorrhage. While the newborn infant, as Clement Smith stated, possesses an unexplained but relative immunity to anoxic damage, this has limits probably not much in excess of fifteen minutes. Doubtless, in many cases, the obstetric difficulties are too great to prevent damage to the infant, and one hesitates to blame the obstetrician for unavoidable risks in desperate situations. Clearly, however, the need of increased oxygen supply to the mother or, at the least, the avoidance of reduced oxygen supply must be constantly kept in mind. Here the serious dangers of nitrous oxide are

of the greatest moment. You will note that this anesthetic is known to have been used in 22 of the 99 cases, and was probably used in others. Eastman has called attention to the serious risks to the baby of nitrous oxide during labor when less than 15 per cent oxygen is given with it, an amount only 75 per cent of that in air at sea level. Unfortunately, with 15 per cent or more oxygen the anesthetic effects of nitrous oxide are considerably lessened. Despite the warnings of Eastman, which must be rather widely known, nitrous oxide continues to be extensively used in the second stage of labor, and in an apparently authoritative manual on anesthesia, published in 1945, the use of mixtures containing only 10 per cent of oxygen is advised for labor pains and a further reduction is advised if necessary "until an efficient mixture is determined." There can be no question that under this scheme the fetus is subjected in many instances to a series of anoxic insults over a period of two hours or more, probably with cumulative effects on the central nervous system. In my opinion, there would be considerably fewer cases of cerebral injury at birth if nitrous oxide were entirely abandoned as an obstetric anesthetic. This is doubtless too much to hope, but the need for 15 per cent or more of oxygen must be more generally recognized and insisted on. Sedation, with barbiturates and other depressants, was recognizably heavy in 6 of the cases. This bears out Schreiber's contention, although oversedation was not one of the most frequent items in the series. The dangers to the infants of oxytocic posterior pituitary extracts have been pointed out by De Lee and more recently by Gustavson and Garceau. They are still commonly used for induction of labor and in the case of overdosage or of idiosyncrasy may cause prolonged uterine systole with reduction in uterine blood flow and oxygen supply. The possible danger of quinine as an oxytocic in producing deafness in the infant was discussed by H. M. Taylor in 1934, and it is interesting that 1 of the children in the series in whose birth quinine was used as an oxytocic has been deaf all his life.

The question of what part intracranial hemorrhage played during the paranatal and neonatal period cannot be answered with accuracy. One infant had hemorrhagic disease of the newborn with symptoms suggestive of intracranial hemorrhage, 2 are known to have had subdural hemorrhages and another is said to have had "increased brain pressure." Unilateral convulsions, observed in 3 cases, suggest subdural hemorrhage. While I believe that intracranial hemorrhage is a far less common cause of cerebral atrophy than simple anoxia, its occurrence and importance are undeniable. Going over the necropsy records of 107 infants born alive and dying during the neonatal period at our hospital, I found that massive hemorrhage, mainly subdural, adequate to explain death was present in 26, or 24.3 per cent of them; minor hemorrhage, insufficient to explain death or injury to the brain and usually associated

with tentorial tears, was present in 22, or 22.4 per cent, while no hemorrhage at all was found in 57, or 53.3 per cent. Ingraham has recently reported that in a series of 98 cases of subdural hemorrhage in infancy 28 could be traced to the neonatal period. The great importance of this type of injury at birth is that if recognized in time it can be remedied, and its sequelae prevented, by operation. Herein pediatricians have a serious responsibility. The simple test of subdural puncture will provide the diagnosis if one is alert to the indications. Operation can be done to advantage during the neonatal period. In 1922 Dr. Towne operated on 1 of our patients at the age of 10 days, found and ligated a ruptured cerebral vein, and the child recovered without known sequelae.

Table 4, showing the condition of the children at birth, reveals the fact that prolonged apnea or cyanosis, requiring resuscitation, occurred in 22. The methods of resuscitation have greatly improved in recent years, and old-fashioned brutal, and relatively ineffective, methods have been widely abandoned, although not universally. Use of the laryngo-

TABLE 4.—*Condition at Birth*

Apparently normal	61
Prolonged apnea or cyanosis	22
Shock	1
Opisthotonos	1
Extreme immaturity (906 Gm.)	1
Immaturity, other degrees	12
Not stated	12

scope for removing under direct vision occluding plugs of mucus is an advance of the greatest importance, and this method is in wider and wider use instead of simple aspiration. The liberal administration of oxygen to infants at birth is now, I believe, in almost general use. It will be noted that 13 children in the series were immature, that is, either delivered before term or weighing less than 2,500 Gm. at birth. The principal danger that such infants run is, I suspect, an anoxic one, which is due to several different factors. The blood has a lower hemoglobin and carbonic anhydrase content than that of full term babies, so that immature babies have a poorer resistance to anoxia; and they are especially apt to have prolonged and repeated attacks of apnea, which in some instances may be caused by intracranial hemorrhage, but in most cases is apparently due to immaturity of the respiratory controls. The relative softness of the thoracic cage and weakness of the thoracic muscles are other contributing factors. It is remarkable, however, how often use of the best modern methods, including clearing of the air-ways, use of oxygen, transfusions and administration of ascorbic acid, will succeed in preventing damage—a pediatric contribution of the greatest importance to the problem under discussion. Neonatal hypoprothrombinemia, fortunately a rare disease, was present in only 1 of the cases.

Theoretically preventable by the administration of vitamin K to mother or infant, a measure which is now almost universally employed, I am somewhat skeptical of its full preventability by this means, since vitamin K had been used in standard dosage for prevention in the last case of the disease which I have seen. Prompt transfusion seems to be a more effective measure, for which the pediatrician must be alert.

The fairly large proportion of cases in the series in which the trouble began during the postnatal period, shown in table 5, was somewhat surprising to me. Infection was responsible for nearly two thirds of the cases, of which about half were due to encephalitis, and nearly all occurred in the first two years. That 5 cases followed pertussis is notable. With reference to preventability, the data bring out the importance of giving gamma globulin for the prevention or mitigation of measles, especially in infants and young children, and of earlier

TABLE 5.—*Postnatal Factors*

Infectious		26
Encephalitis	13	
Measles	4	
Equine	3	
Unspecified	6	
"Meningitis," type unspecified	3	
Pertussis	5	
Pneumonia	3	
Laryngeal diphtheria	1	
High temperature with convulsions	1	
Noninfectious		13
Convulsions, severe, cause unknown	6	
Trauma to head (falls, blow)	4	
Intracranial hemorrhage (cause unknown)	1	
Prolonged apnea, cause unknown	1	
Apnea and cardiac arrest from "mecholyl"	1	

vaccination against pertussis. The use of hyperimmune serum for the treatment of pertussis in infancy and early hospitalization of infants with the disease so that oxygen and other suitable measures can be applied promptly would probably reduce the number of cerebral accidents to which such patients are subject. I may also mention the encouraging fact that in my community at least pertussis has become rather infrequent since vaccination against it has been widely employed. It is of interest to note that 3 cases of cortical atrophy followed severe pneumonia, a sequence which modern chemotherapy and antibiotics may be expected to make less frequent.

Of the noninfectious factors, trauma to the head is the most important of the preventable group, since intracranial hemorrhage, probably subdural, was unrecognized and untreated before it was too late. Herein, the great importance must be stressed of watching carefully and for a sufficient period, with subdural hemorrhage in mind, those children who have suffered injuries to the head, since gradually increasing intracranial pressure may at first produce only rather indefinite symptoms in infants

and young childen, as Ingraham has emphasized. The single case of drug reaction deserves comment. This occurred in a boy of 9 months with congenital megacolon, who was given 4 mg. of "mecholyl chloride" N. N. R. intramuscularly, when smaller amounts had previously failed to produce the desired effect on peristalsis. Apnea was followed three minutes later by cardiac arrest. Artificial respiration and an injection of epinephrine revived him. The total period of anoxia was not recorded but could not have been much less or more than five minutes. When first seen by me three months later, he was unable to sit up or to respond to ordinary stimuli, and had generalized cortical atrophy: an example of the selectively damaging effects of comparatively brief anoxia on the brain.

I have reviewed the series case by case in the hope of determining in how many the damage was probably or possibly preventable. Dealing with histories that too often failed to give the whole story, that certainly left out important details in many instances, I have found any really accurate appraisal impossible, but in about one fifth of the cases the data suggest the probability, and in about one fourth a more remote possibility, of prevention, while in about 40 per cent it was obvious that nothing preventable could have been done. In the remainder, information was too incomplete to permit any judgment.

My impression, obtained from the study as a whole, is that better obstetrics and better pediatrics could have prevented a considerable part of these disasters merely if the present day knowledge had been applied. While more knowledge and improved technics are needed, and the search for them must continue, there is also need of a much wider dissemination and adoption into practice of the knowledge of basic principles and technics already available. There is need of more conferences between obstetricians and pediatricians on the topic of today's discussion. There is need of an authoritative formulation, by all persons in the medical profession who can contribute to the problem, of minimum standards of practice for the protection of fetus, infant and child against those things that threaten the organic integrity of the central nervous system. There is need of more and better education, both at the undergraduate and the postgraduate level. Not until more physicians responsible for maternal and child care are fully aware of their responsibilities and are equipped properly to deal with them, can one expect to reduce the incidence of these injuries to the brain which constitute one of the great tragedies of life.

EARLY IMMUNIZATION AGAINST PERTUSSIS

J. M. ADAMS, M.D.

A. C. KIMBALL, Ph.D.
AND
F. H. ADAMS, M.D.
MINNEAPOLIS

THE SEVERITY and relatively high mortality of whooping cough in early life make effective immunization desirable. The following preliminary studies were designed to investigate the possibilities of protecting infants during the first six months of life against pertussis. We were also interested to learn more about the general mechanism of production of antibody by young infants. Sauer [1] reported studies in 1941 on the age factor and concluded that immunization should be undertaken after the seventh month because of the degree of failure to protect the infant prior to the third month as opposed to the seventh month. He found that "although some infants at the age of 3 months possess the power to elaborate specific antibody . . . others seem to lack this power." Our studies based on the ability of the infant's serum to agglutinate live phase I organisms showed the same inability on the part of some infants to form specific antibody. Sako and his co-workers [2] have recently reported success in the early age period, demonstrating that 75 per cent of young infants exhibited antibody responses as measured by agglutination tests. They suggested further on the basis of follow-up studies on the incidence and severity of pertussis in the immunized and nonimmunized groups that early protection against whooping cough is practicable.

Sauer [3] in his most recent chapter (1946) stated that "the earliest age at which most infants developed pertussis antibodies from three doses of plain vaccine was the sixth or seventh month of life." Our studies

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From the Department of Pediatrics, University of Minnesota Medical School and the Minnesota Department of Health, Division of Preventable Diseases.

1. Sauer, L. W.: The Age Factor in Active Immunization Against Whooping Cough, Am. J. Path. **17**:719, 1941.

2. Sako, W.; Treuting, W. L.; Witt, D. B., and Nichamin, S. J.: Early Immunization Against Pertussis with Alum Precipitated Vaccine, J. A. M. A. **127**:379 (Feb. 17) 1945.

3. Sauer, L. W.: Whooping Cough, in Brennemann, J.: Practice of Pediatrics, Hagerstown, Md., W. F. Prior Company, Inc., 1946, chap. 34.

in part confirm this observation, although after monthly inoculations completed at 3 months of age some significant rise of titer was evident by the fourth month. However, we did observe rapid responses to weekly inoculations given during the first month of life, a few of the infants showing a relatively high titer at the age of 1 month. One infant showed a titer of 1 to 1,280 at the age of 6 weeks.

METHODS AND OUTLINE OF STUDY

A group of mothers and babies were selected which could be followed at approximately monthly intervals throughout the first year of the infants' life. Infants were given three inoculations, consisting of phase I superconcentrate vaccine,[4] 2.5 cc. (40,000,000,000 organisms per cubic centimeter), or a total dose of 100,000,000,000 organisms given at weekly or monthly intervals. The dosage schedule was 0.5 cc., 1 cc. and 1 cc. Mothers who were immunized during the last trimester of pregnancy were given three inoculations at two week intervals, for a total of 100,000,000,000 organisms.

The obtaining of the blood sample from infants was accomplished easily by means of a small glass tube, a cross section of which is shown in figure 1 (about two-thirds actual size).

Fig. 1.—Tube for obtaining blood samples. It is made as follows: A 6 to 8 inch (15.2 to 20.3 cm.) length of ¼ inch (0.64 cm.) soft glass tubing is heated in the middle, pulled out and broken. The pointed end is sealed by heating in the flame; the base end is closed in the same way. The tube is then held in the side of the flame at one point and a hole soon appears at the site.

The tip of the tube is cracked off and applied to the puncture in the heel or the toe. When the tube is held at a 45 degree angle the blood runs into its base. After clotting of the blood, the tube is filled at the point indicated by the arrow, is centrifuged, and the serum is removed for testing.

A small study of the Hemophilus pertussis in agglutinating titers of colostrum was done on 30 samples. Untreated specimens are too opaque to be satisfactory for tube agglutination tests. After considerable experimentation, two methods were finally used and found to be satisfactory, especially for three day colostrum. Most of the two day samples were unsatisfactory with either method.

METHOD 1: *Clarification with Ether.*—Equal parts of colostrum and ether were well mixed with a pipet and the mixture centrifuged at about 1,500 revolutions per minute for five minutes. The ether-

4. The vaccine was furnished on request by Cutter Laboratories, Berkeley, Calif.

colostrum emulsion was thus separated into two layers. The lower, watery layer was used for the agglutination tests.

METHOD 2: *Clarification by Seitz Filtration.*—Colostrum was diluted 1 to 2.5 with sterile 0.9 per cent solution of sodium chloride and clarified with Seitz filters. Small filters holding 2.0 cc. samples and employing centrifugal force were the type used.

Either one of these treatments might remove antibody from colostrum. As a check on the possibility, rabbit antiserum against H. pertussis was added to samples of colostrum before treatment. As measured by the agglutination test, there was no detectable loss in the added H. pertussis antibody with either method of treatment. For the agglutination tests 0.5 cc. of serum or treated colostrum diluted 1 to 10, 1 to 20, 1 to 40, and so forth, with saline solution was used with 0.5 cc. of live phase I H. pertussis antigen. Tests were incubated at 37 C. in a water bath overnight and refrigerated two to four hours before reading. The final dilutions were 1 to 20, 1 to 40, 1 to 80, and so forth. Final dilutions are recorded as the titer. Each lot of antigen was studied prior to use with negative serums and rabbit antiserums against H. pertussis of known titer. Only those antigens were used which were similar in sensitivity with this test method. Over eight hundred agglutination tests were done on the mothers' and infants' serums and colostrum with phase I live H. pertussis antigen. These tests were all performed by one of us (A. C. K).

The study was divided into several parts in order to learn as much as possible about the ability of the young infant to form antibodies. The following groups were studied:

I. Control; mothers and infants not immunized.
II. Infants given three weekly inoculations within the first month of life
III. Infants given three monthly inoculations prior to the fourth month of life
IV. Infants on a high protein diet given three weekly or monthly inoculations
V. Mothers immunized during pregnancy; titer of the infants' serums determined at intervals up to six months
VI. Study of placental transfer of mother's antibody to cord blood
VII. Study of colostrum antibody

RESULTS

I. The first group served as a control included 7 babies, who were followed at approximately monthly intervals. Thirty-three determinations were made on the serums of these subjects. Although 2 subjects were born with low titers (1 to 80 and 1 to 20), these titers fell to zero by 2 weeks of age. All subsequent determinations were negative.

II. The second group included 21 babies, who were given a total of sixty-four inoculations at weekly intervals. For all but 4 they were

completed before 1 month of age. Six subjects failed to show any rise in titer when followed at approximately monthly intervals. The remaining subjects did show definite rises in titer, and 5 of 9 subjects tested had good titers established as early as 1 month of age. The mean titer at 1 month was 1 to 160. At 6 weeks of age 1 baby had a titer of 1 to 1,280. The mean levels tended to drop rapidly, as illustrated by the one hundred and sixteen determinations on the graph in figure 2.

III. The third group included 19 babies, who were given a total of fifty-seven inoculations at approximately monthly intervals. For all but 8 they were completed prior to the third month of life. Five subjects failed to show any rise of titer. The remainder showed titers but at a much slower rate than the previous group. One baby at 3 months of

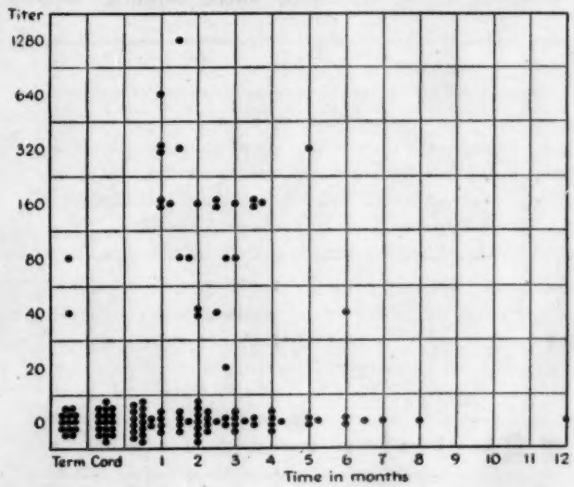

Fig. 2.—Antibody responses of 21 infants following weekly inoculations prior to 1 month of age.

age had a titer of 1 to 160; the mean, however, at 4 to 5 months was 1 to 80. These ninety-nine determinations are shown on the graph in figure 3.

IV. Recent studies have indicated the importance of protein in the formation of antibody. By providing extra protein to the rapidly growing infant, it was considered of interest to determine whether the antibody responses might not be favorably affected. Ten babies were fed supplements of protein in the form of "casec" during the first two months of life, at which time strained beef [5] was added to the diet. At 3 months of age, the "casec" was reduced and the beef increased. Egg was added at 4 months of age. The diets were carefully calculated and

5. The strained beef was furnished on request by Swift & Company, Chicago.

sufficient "casec," beef and egg protein were added to double the daily protein intake of these babies as compared with that of the babies in the other groups.

The results of this small study were negative. We were unable to demonstrate an increase in the agglutinating response as a result of doubling the intake of protein. In fact, the responses on the whole were less than those of infants who received a normal diet. Two babies who received weekly inoculations on the aforementioned schedule did show titers of 1 to 160 at the age of 1 month, but by the age of 2 months these titers had again fallen to zero. Half of the subjects who received the diet high in protein failed to show any response of agglutinating antibodies with the method used.

V. The fifth group comprised 16 mothers and their babies. All of the mothers received three injections each, totaling 100,000,000,000

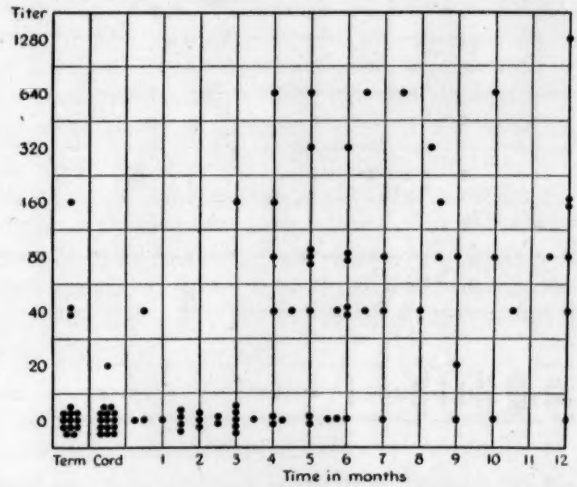

Fig. 3.—Antibody responses of 19 infants following monthly inoculations most of which were given prior to 3 months of age.

killed organisms during the last trimester of pregnancy, the program being completed a month before term in nearly all instances. Sixty-eight determinations were made on the mothers at term, on the cord blood and on the babies during the first six months of life. The mean titer of the mothers at term was 1 to 320. The mean titer of the specimens of cord blood was 1 to 160. During the first six months of life the titer was gradually lost. At 2 months of age the mean titer was 1 to 80. In the mothers in every instance some titer developed, but 3 of the babies failed to show any agglutinating titer in the cord blood. In 2 instances the cord blood had a higher titer than that of the corresponding mother. The results of determinations on the specimens obtained at term from the mothers and on the corresponding cord bloods are recorded in table 1.

In order to test the possibility that some active immunity might have developed in utero in the babies of immunized mothers, we selected 2 babies whose mothers had established a good titer at term (1 to 320

TABLE 1.—*Results of Determinations on Specimens of Maternal and Cord Serum, Expressed in Denominators*

Number	Term	Cord
1	80	160
2	320	0
3	40	0
4	320	160
5	1,280	160
6	40	0
7	320	320
8	2,560	1,280
9	80	0
10	640	320
11	320	320
12	320	320
13	40	160
14	320	160
15	1,280	1,280
16	160	160

TABLE 2.—*Results of Determinations on One Hundred and Forty-Two Specimens of Antepartum and Cord Blood; Range of Titers for Each Group is Expressed in Denominators*

Antepartum	Cord	Number	Percentage
Negative	Negative	109	76.8
20-40	20-40	4	2.8
80-320	20-160	11	18.3
20-160	Negative	15	
0-80	40-160	3	2.1

TABLE 3.—*Comparison of Titers of Blood and Colostrum*

Number	Antepartum	Cord	Colostrum	
			Ether	Seitz Filtration
1	2,560	...	320	320
2	320	320	80	40
3	80	160	20	40
4	80	—	—	—
5	..	20	—	—
6-14	—	—	—	—

in each), and the cord blood titer was 1 to 320 in one and 1 to 160 in the other. Neither of these babies received any inoculation after birth. They had no titer at 1 year of age. We gave each baby 1 cc. of antigen (40,000,000,000 organisms per cubic centimeter) and followed the titer of the blood serum at 1 week and again three weeks after the single inoculation. No titer developed in either baby in three weeks' time.

IV. One hundred and forty-two pairs of specimens of antepartum and cord blood were tested. Negative results for both specimens were obtained in 109 pairs, or 76.8 per cent. Four pairs gave positive results at the same low titer (20 to 40). The titer of the specimen of cord blood was lower than the titer of the sample of antepartum blood in 26 cases, or 18.3 per cent. In this group of 26 pairs of specimens the specimens of cord blood gave weaker positive results in 11 cases and negative results in 15 cases. The titer of the cord blood was higher than of the mother's antepartum blood in 3 cases. These results are given in table 2.

VII. We tested 30 samples of colostrum after clearing of the specimens by two methods, ether extraction and Seitz filtration. A correlation titer of the colostrum and of the available specimens of antepartum and cord blood is recorded in table 3.

COMMENT

The importance of early immunization against pertussis was thoroughly emphasized by Sako and his associates [2] in their recent paper by means of figures from the mortality statistics of the United States Census Bureau. Sixty-seven per cent of all the deaths occur in the first year of life. Sauer [1] and Sako [2] have both shown fairly good results as a consequence of early immunization, and although protection is far from perfect, it appears to be a safe and practical procedure. The reactions to the inoculations were inconsequential. The fact that the infant at 7 months of age is able to respond to immunization better than the newly born infant is rather weak evidence for withholding the immunization past the age of greatest risk. In private practice withholding immunization until 7 months may be warranted only if the infant can be protected from exposure by a controlled environment. However, in public health preventive programs an earlier period would seem desirable. Furthermore, it is a well recognized principle of epidemiology that the nonimmunized persons in a group derive protection from existing in a well immunized population. Thus the few infants who fail to respond to the vaccine are indirectly protected.

Sako and his co-workers' data [2] indicate that good correlation exists between the agglutinating ability of the patient's serum and immunity. None of their patients who had a strong agglutination (qualitative method) contracted pertussis, and the majority who acquired the disease in a mild form after immunization were those babies who failed to show any agglutination. Miller and his associates [6] also suggested that susceptibility does not occur in the presence of agglutinins in high titer. Our studies were based entirely on quantitative tube agglutination tests.

6. Miller, J. J., Jr.; Humber, J. B., and Dourie, J. O.: Immunization with Combined Diphtheria and Tetanus Toxoids (Aluminum Hydroxide Adsorbed) Containing Hemophilus Pertussis Vaccine, J. Pediat. **24**:281, 1944.

The rapid agglutinating response in the group of babies given weekly inoculations was most surprising. We know of no work which shows a similar response; in fact, the weekly interval of inoculation has been condemned because of the poor responses following its use. It is a method, however, of producing a rapid titer in early infancy in the majority of babies inoculated. It seems most logical that if antigen were continued at monthly intervals for the early months of infancy the titer level could be maintained. This remains to be done. The mechanism of this rapid response is as yet unexplained. If the site of formation of antibody is in the lymphocytes, as has been recently shown by several workers,[7] it seems possible that the infant in utero might have the potential to manufacture some antibody substance and not be wholly dependent on passive transfer. We hope to pursue this interesting hypothesis further.

Although Cannon and his co-workers [8] showed clearly that protein-depleted animals, as compared with normal controls, possessed little ability to manufacture antibodies, we were unsuccessful in augmenting the infants' capacity to form antibodies by feeding excess protein. Young animals are unable to form the same quantity or quality of antibody as older animals.[9] The growth demands of the infant for protein are undoubtedly great, at a time when his weight is doubling, suggesting that insufficient amounts were available for formation of antibody. That this apparently does not obtain is indicated by our results in this group.

At birth the infant of an immunized mother has an agglutinin titer almost as high as its mother's, and this titer gradually drops to zero over a period of a few months. Several studies have reported similar observations at the time of birth but have not followed the infant's titer, as we did in this group of 16 mothers and babies.

The antibody content of colostrum has been studied by several workers. Theobald Smith and Little [10] first pointed out the immunologic significance of colostrum for the newborn calf. The human placenta, in contrast to the bovine, however, readily permits the passage of the

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7. Dougherty, T. F.; Chase, J. H., and White, A.: Pituitary-Adrenal Cortical Control of Antibody Release from Lymphocytes: An Explanation of the Anamnestic Response, Proc. Soc. Exper. Biol. & Med. **58**:135, 1945. Ehrich, W. E., and Harris, T. N.: The Site of Antibody Formation, Science **101**:28, 1945.

8. Cannon, P. R.; Chase, W. E., and Wissler, R. W.: The Relationship of the Protein Reserves to Antibody Production: The Effects of a Low Protein Diet and of Plasmaphoresis on the Formation of Agglutinins, J. Immunol. **47**: 133, 1943.

9. Freund, J.: The Influence of Age upon Antibody Formation, J. Immunol. **18**:315, 1930. Baumgartner, L.: Age and Antibody Production, ibid. **27**:407, 1934.

10. Smith, T., and Little, R. B.: The Significance of Colostrum to the Newborn Calf, J. Exper. Med. **36**:181, 1922.

globulin molecule, and therefore the infant is born with antibody titers slightly under those of its mother. Debré and Ramon [11] tested colostrum for tetanus antitoxin in previously immunized mothers. Diphtheria antitoxin has also been similarly investigated by several workers.[12] We know of no previous studies on H. pertussis antibodies in colostrum. Results of our investigations were similar to the results obtained by the aforementioned workers. H. pertussis antibody is present but in lower titer than is found in the maternal or cord blood. Antibodies in colostrum probably play a minor role in immunity if the placenta is permeable to the antibody of the mother.

SUMMARY

The importance of early immunization against pertussis is reemphasized, and although success is not possible in all infants, it is a safe and practical procedure. Our studies were not large enough to permit definite conclusions. However, it appears that with weekly inoculations, good antibody titers can be demonstrated in over half of the infants by the age of 1 month to 6 weeks. Monthly inoculations give a slower but more permanent rise. A combination of the two procedures might offer the best chance of early protection to the infant.

Protein deficiency definitely interferes with production of antibody in the animal, as shown by others. Increased dietary protein does not appear to play a role in enhancing production of antibody.

By immunizing mothers in the last trimester of pregnancy we were able to show, as others have, that the specimen of cord blood contained antibodies, but in somewhat lower amounts than the mother's serum. This antibody titer is gradually lost by the infant during the first six months of life.

The results of our determinations on 142 pairs of specimens of antepartum and cord blood from unimmunized mothers showed that in 77 per cent H. pertussis antibodies were entirely absent.

Colostrum contains antibodies against pertussis, but their significance in the human being is probably negligible. Methods for their determination are outlined.

An easy method for collecting blood samples from infants for agglutination studies is described.

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11. Debré, R.; Ramon, G., and Thirotoix, P. L.: Le colostrum des femmes vaccinées contra le tétanos ne contient pas d'antitoxine tétanique, Compt. rend. Soc. de biol. **103**:383, 1930.

12. Kuttner, A., and Ratner, B.: The Importance of Colostrum to the New-Born Infant, Am. J. Dis. Child. **25**:413 (June) 1923. Sugg, J. Y.: Diphtheria Antitoxin in the Milk of a Highly Immune Mother, Am. J. Hyg. **22**:227, 1935. Liebling, J., and Schmitz, H. E.: Colostrum as Source of Diphtheria Antitoxin in Actively Immunized Pregnant Mothers, J. Pediat. **22**:189, 1943.

ORAL ADMINISTRATION OF PENICILLIN IN PEDIATRICS

HENRY A. REISMAN, M.D.
JAMAICA, N. Y.
AND
ARTHUR A. GOLDFARB, M.D.
AND
MOLLY MOLLOY, M.S.
NEW YORK

PART 1

A. INTRODUCTION

AT PRESENT there are many commercial preparations of penicillin for oral use. Unfortunately, there are conflicting opinions as to its efficacy. This is evidenced in part by the existing disagreement in the literature and likewise by the lack of uniformity of directions for dosage and administration.

Several children have been admitted to the wards of Queens General Hospital with advanced pyogenic diseases of various types after ineffective oral treatment with penicillin at home. The causative organisms in these cases frequently are made more resistant to penicillin administered parenterally by inadequate oral treatment. This form of treatment does more harm than good. Preparations of penicillin for oral administration are being used for the initial treatment of these patients, despite the fact that the Food and Drug Administration has approved oral use of this drug only for cases in which the disease is already "under control" after parenteral treatment. The hazards of administration of sulfadiazine and related drugs and the practical difficulties encountered in the parenteral use of penicillin are obvious and give impetus to a search for some effective enteral method of administration of penicillin.

B. HISTORICAL BASIS

Originally Rammelkamp and Keefer [1] and Rammelkamp and Helm [2] showed that gastric juices inactivate penicillin. Recently other investi-

From the Department of Pathology and the Department of Pediatrics, Queens General Hospital, Jamaica, N. Y.

1. Rammelkamp, C. H., and Keefer, C. S.: The Absorption, Excretion, and Distribution of Penicillin, J. Clin. Investigation **22**:425 (May) 1943.

2. Rammelkamp, C. H., and Helm, J. D.: Studies on the Absorption of Penicillin from the Stomach, Proc. Soc. Exper. Biol. & Med. **54**:324 (Dec.) 1943.

gators [3] claimed that the loss in oral ingestion of penicillin is primarily due to the inability of the gastrointestinal tract to absorb penicillin and that there is, eventually, destruction of a good deal of the residual penicillin by the penicillinases produced by organisms in the bowel.

The present attempts to achieve a maximum effect from orally ingested penicillin may be tabulated as follows:

(1) Protecting the penicillin from the gastric acid by
  (*a*) Using a buffer to overcome the acidity [4]
  (*b*) Putting the penicillin in an enteric-coated capsule [4d]
  (*c*) Mixing the penicillin with protective fats or oils [5]
  (*d*) Adsorbing the penicillin onto a special buffering chemical [6]
(2) By giving the oral penicillin at stated time intervals to obtain maximum absorption or minimum loss or both [7]
(3) By using a more stable (or more absorbable) penicillin product or chemical form of penicillin [8]
(4) By giving a much larger ingested dose than would have to be absorbed to overcome the amount lost [3b]

Whether or not gastric acidity is an important factor is still being discussed.[3]

C. PLAN OF STUDY

We were granted a large quantity of "oral penicillin" [9] containing the buffers aluminum hydroxide, calcium carbonate and magnesium oxide. The Food and Drug Administration had granted license for

3. (*a*) Finland, M.; Meads, M., and Ory, E. M.: Oral Penicillin, J. A. M. A. **129**:315 (Sept. 29) 1945. (*b*) McDermott, W., and others: The Absorption of Orally Administered Penicillin, Science **103**:359 (March 22) 1946.

4. (*a*) Charney, J., and others: Urinary Excretion of Penicillin in Man After Oral Administration with Gastric Antacids, Science **101**:251 (March 9) 1945. (*b*) Seeberg, V. P., and Collen, M. F.: Calcium Carbonate as an Antacid for Oral Penicillin, ibid. **102**:225 (Aug. 31) 1945. (*c*) Burke, F. G.; Ross, S., and Strauss, C.: Oral Administration of Penicillin: Preliminary Report, J. A. M. A. **128**:83 (May 12) 1945. (*d*) György, P., and others: Administration of Penicillin by Mouth: Preliminary Report, ibid, **127**:639 (March 17) 1945.

5. Libby, R. L.: Oral Administration of Penicillin in Oil, Science **101**:178 (Feb. 16) 1945. Perlstein, D., and others: Oral Administration of Penicillin in Corn Oil and Lanolin, ibid. **102**:66 (July 20) 1945.

6. Welch, H.; Price, C. W., and Chandler, V. L.: Prolonged Blood Concentrations After Oral Administration of Modified Penicillin, J. A. M. A. **128**:845 (July 21) 1945.

7. Finland, Meads and Ory.[3a] Ross, S.; Burke, F. G., and McLendon, P. A.: Penicillin by Mouth: Report of Clinical Trial, J. A. M. A. **129**:327 (Sept. 29) 1945.

8. Cavallito, C. J., and others: The Benzyl Ester of Penicillin, Science **102**: 150 (Aug. 10) 1945. Gamble, T. O.; Miller, L. C., and Tainter, M. L.: Benzyl Penicillin: Clinical Toxicity and Efficacy by Mouth in Impetigo in Newborn Infant; Preliminary Report, Am. J. Obst. & Gynec. **50**:514 (Nov.) 1945.

9. The penicillin was supplied by Hoffmann-LaRoche, Inc.

marketing of this product but limited its indications as previously stated and for use in gonorrhea.[10]

Because of the advantages possible with such a product we decided to investigate its use in children with severe infections which are usually pyogenic in character without previous parenteral administration of penicillin.

The patients chosen were acutely ill patients from the pediatric wards of the Queens General Hospital. They were seen twice daily by one of us and their progress carefully noted. In general their diseases were diagnosed as severe infections of the ear, the nose, the throat, the larynx or the bronchi of the type which one would undoubtedly treat with sulfadiazine administered orally in the days before penicillin.

One immediate effect of our study was, therefore, a comparison of the practical efficacy of penicillin versus sulfadiazine when administered orally.

It was originally planned to culture the offending bacterial organism in each case and first determine its sensitivity to penicillin. However, this procedure in the treatment of diseases of the nose, the throat and the bronchi is often of no practical value, since one must often rely on a "predominant" organism because many different, potentially pathogenic, organisms are frequently found in these anatomic areas. In private practice, the physician does not, as a rule, have the luxury of a bacteriologist's aid in the home. It is here that oral administration of penicillin should be of the greatest value.

The patients did receive, as part of a careful follow-up, routine blood counts, urinalysis, tuberculin tests, routine roentgenograms of the chest and blood cultures and any other technical procedures necessary. Levels of penicillin in the blood were noted at varying intervals during the patient's waking hours to determine the blood level with various methods and dosage.

D. METHOD USED AND ITS RATIONALE

The penicillin was given orally in a manner which we thought at the time the most practical both for the home and the hospital. Our first group of patients were treated every two hours day and night. The medication was given regardless of the feeding schedule. Others were treated every hour during the day and every two hours during the night. Later some patients were treated every hour "around the clock." This is the same rationale that Bunn and his colleagues[11]

10. Keefer, C. S., and others: New Dosage Forms of Penicillin: Statement Concerning Certifiable Penicillin Products Including Recommended Indications, Dosages and Precautions, J. A. M. A. **128**:1161 (Aug. 18) 1945.

11. Bunn, P. A., and others: Treatment of Pneumococcic Pneumonia with Orally Administered Penicillin, J. A. M. A. **129**:320 (Sept. 29) 1945.

Results of Clinical Series of Treated Patients

Name of Disease	Case Number	Results *	Blood Levels †	Oxford Units Total Dosage	Oxford Units Dosage plan	Days Treated	Comment
I. Acute tonsillopharyngitis (4 cases)	1	F	E	2,150,000	50,000 every hour in daytime, and every 2 hours at night	4	
	2	F	C	2,300,000	100,000 every hour in daytime, and every 2 hours at night	2	
	3	F	E	3,300,000	100,000 every hour in daytime, and every 2 hours at night	2	
	4	F	E	7,800,000	1,000,000 every hour while awake and every 2 hours while asleep	5	
II. Acute hemolytic streptococcic tonsillopharyngitis	1	P	E	4,750,000	50,000 every hour in daytime, and every 2 hours at night (to 2,450,000 and stopped); resumed at 100,000 every hour in day and every 2 hours at night	4	Cleared only after penicillin was cut and sulfadiazine treatment started
III. Acute tonsillopharyngitis with acute sinusitis	1	F	E	5,000,000	100,000 every hour in daytime, and every 2 hours at night	3	
IV. Acute tonsillopharyngitis with ulcerative stomatitis (2 cases)	1	F	B	2,000,000	50,000 every hour for 10 doses and then 50,000 every 2 hours	6	
	2	F	D	2,350,000	.....	6	
V. Acute tonsillopharyngitis with sinusitis and otitis media (2 cases)	1	F	E	1,400,000	50,000 every 2 hours while awake and asleep	3	
	2	P	E	10,800,000	100,000 every hour while awake and every 2 hours while asleep	6	Began to clear after 2 days on sulfadiazine; no response previously
VI. Acute tonsillopharyngitis with otitis media (4 cases)	1	P	E	7,150,000	50,000 every 2 hours during night for 6 doses and 100,000 every hour during day thereafter and 1,000,000 every 2 hours during day thereafter	5	
	2	F	E	2,600,000	100,000 every hour while awake and every 2 hours while asleep	2	
	3	F	E	5,400,000	1,000,000 every hour while awake and every 2 hours while asleep	3½	

		4	P	B	5,600,000	100,000 every hour while awake and every 2 hours while asleep	4	
VII.	Acute tonsillopharyngitis with bronchitis (1 case)	1	P	E	1,700,000	50,000 every hour during day and every 2 hours during night	3	
VIII.	Infectious mononucleosis, severe (2 cases)	1	F	A	1,400,000	50,000 every 2 hours	2½	Heterophilic agglutination; fever came down rapidly and membranes cleared rapidly from tonsils; spleen subsided rapidly; afebrile within 3 to 4 days
		2	F	A	1,800,000	50,000 every 2 hours	2½	
IX.	Tracheobronchitis (croup), tonsillopharyngitis and otitis media (1 case)	1	P	E	2,425,000	50,000 every 2 hours	6	Child had convulsions; fever continued irregularly
X.	Acute tracheobronchitis with tonsillopharyngitis (1 case)	1	P	E	2,350,000	50,000 every 2 hours	4	
XI.	A typical pneumonia with acute tonsillopharyngitis (1 case)	1	P	E	1,000,000	100,000 every hour	½	Discontinued when roentgenograms taken revealed a typical pneumonia
XII.	Measles with acute tonsillopharyngitis, cervical adenitis and otitis media (1 case)	1	P	E	3,500,000	100,000 every hour	1½	
XIII.	Acute exacerbation and chronic sinusitis (1 case)	1	P	E	600,000	50,000 every 3 hours	2	No effect; discontinued
						Total penicillin used: 75,375,000 Average per case: 3,426,130		

Summary of table:
Results:
10—poor or no effect
12—fair or some effect
0—good

Blood levels:
2—excellent
2—good
2—fair
1—trace
15—no blood level

* Code for results: good, G; fair or some effect, F; poor or no effects, P.
† Code for blood levels: A, 1 Oxford unit per cubic centimeter of blood serum or over—excellent; B, 0.1 to 0.9 unit per cubic centimeter—good; C, 0.3 to 0.09 unit per cubic centimeter—fair; D, trace to 0.08 unit; E, none.

used in treating their patients. It seemed to be the simplest method, and we used it despite previous claims [4c] that penicillin should be given one half hour before each meal and at least two or three hours after each meal for optimum absorption.

However, in support of the "around the clock" method which we used (regardless of food) were those claims [12] that penicillin given orally gave sustained blood levels, and the claims of others [4] that a buffer would protect the penicillin given orally despite meals or gastric acidity. There were still others who wrote [13] that absorption was gradual and slow when the drug was given orally, and, on the other hand, cumulative and lasting. On this basis the nullifying effects of three meals a day would not be apparent over a twenty-four hour period when buffered penicillin was used and fed continually at regular intervals throughout the day.

The diversified opinions in the literature stimulated us to try one method and watch our results.

E. RESULTS OF OUR CLINICAL SERIES OF TREATED PATIENTS

We found that despite large doses neither our penicillin blood levels nor our clinical results were encouraging. These can be seen in detail in the table.

There were thirteen variations of ear, nose, throat and respiratory conditions treated in 22 cases. Ten cases showed no effect of treatment with large oral doses of penicillin and 12 cases showed fair results. No good results were seen. The fair results reported were, on the whole, in the cases of milder disease, in some of which there might have been a response to nonspecific therapy. Certainly the results were not nearly so good as one might expect from use of sulfadiazine orally in similar circumstances.

The blood levels in 2 were excellent. In both of these cases there was a dramatic response (the 2 cases in section VIII of the table). However, the diagnosis eventually made was infectious mononucleosis. The blood levels here might have been related to the fact that both these patients ate and drank poorly during their first two days of hospitalization, since they were extremely toxic. Similarly the 2 patients we list as having "good" levels (the first case in section IV and the fourth in section VI of the table) had poor fluid and food intakes.

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12. Free, A. H., and others: The Urinary Excretion of Penicillin After Oral Administration to Normal Human Subjects, Science **100**:431 (Nov. 10) 1944.

13. Free and others.[12] Welch, Price and Chandler.[6] Krantz, J. C., Jr.; Evans, W. E., Jr., and McAlpine, J. G.: Oral Penicillin with Basic Aluminum Aminoacetate, Science **101**:618 (June 15) 1945. Penicillin by Mouth, Current Comment, J. A. M. A. **127**:991 (April 14) 1945.

Fifteen patients had no blood level at all that was demonstrable during the daytime. With oral doses as high as 100,000 Oxford units, poor blood levels and unsatisfactory clinical results were obtained.

It can be seen that most cases with poor clinical results had poor blood levels and vice versa. Occasionally cases with fair blood levels showed poor clinical results probably because of the resistance of the organisms involved. The blood levels demonstrated were probably ineffective for about two thirds of the cases. Effective penicillin blood levels should be at least above 0.03 to 0.05 Oxford unit per cubic centimeter of serum.

Our poor results are probably due to inadequate therapy through the oral route with low blood levels. Our low levels of penicillin in the blood substantiate this opinion.

This fact may have been due to destruction of the penicillin, as we gave it, by gastric acidity, or to some factor in the food present in the stomach. It may have been due for some unknown reason to an intrinsic inability of the gastrointestinal tract to absorb most of the penicillin which we used.

It has been shown [14] that the p_H of the stomach contents varies tremendously from time to time and depends ultimately on a great variety of factors such as food, emotion, state of health, time of day and the particular person involved. Therefore it must be apparent that the amount of destruction of penicillin given orally by gastric acidity must vary. It has not been established exactly what proportion of the penicillin in the stomach and various parts of the intestine is capable of being absorbed into the blood. The levels of penicillin in the blood did not reach effective height despite the use of so-called protective buffer substances in an attempt to regulate the variable gastric acidity.

F. UNTOWARD REACTIONS AND DANGERS

We saw three toxic reactions which were similar to those already reported.[15] Two were urticarial eruptions. The most interesting was the third case which occurred in one of our adult controls (Part II) who, while in the tropics as an army officer, had had a fungus infection

14. (*a*) Wolman, I. J.: Study of Fasting Secretions and of Physiologic Responses to "Hard Curd" (Pasteurized) and "Soft-Curd" (Homogenized) Milks, Am. J. Dis. Child. **71**:394 (April) 1946. (*b*) Best, C. H., and Taylor, N. B.: The Physiological Basis of Medical Practice, ed. 3, Baltimore, Williams & Wilkins Company, 1943, pp. 711-750 and 813-816.

15. (*a*) Morris, G. E., and Downing, J. G.: Bullous Dermatitis (Dermatitis Medicamentosa) from Penicillin, J. A. M. A. **127**:711 (March 24) 1945. (*b*) Sensitivity of Bacteria to Penicillin, Current Comment, ibid. **127**:1131 (April 28) 1945. (*c*) Graves, W. N.; Carpenter, C. C., and Unangst, R. W.: Recurrent Vesicular Eruptions Appearing During Administration of Penicillin, Arch. Dermat. & Syph. **50**:6 (July) 1944.

of the skin which had completely cleared months before. The oral use of penicillin by him precipitated an acute exacerbation of the condition with pronounced generalized erythema, especially in blotchy areas over the face and in the crural area. It was associated with severe pruritus. It cleared forty-eight hours after cessation of use of the drug and was followed by some exfoliation of the skin in the affected areas.

Though other reactions to penicillin are rare, they do occur. Chills, fever, headache, urticaria, gastrointestinal disturbances and vesicular dermatitis [15c] occur, as does bullous dermatitis.[15a] Delayed sensitization in a patient who was asthmatic has been reported,[15c] and in this particular patient a severe allergenic reaction resulted simulating serum sickness.

Feinberg [16] pointed out that 6 per cent of allergic patients are sensitive to the pollen of the penicillin family and that the reaction to the scratch test is positive in these 6 per cent. Penicillin spores constitute 11 per cent of the spore content of the Midwest.

Development of resistance to penicillin among certain strains of staphylococci and other organisms requiring high blood levels does occur.[17] Of one hundred and eight strains of staphylococci examined by Gallardo,[18] 22 per cent either were naturally resistant or became resistant during inadequate treatment. According to him, about 9.4 per cent of pathogenic strains acquire resistance during inadequate treatment. The latter fact emphasizes the importance of adequate initial high dosage to maintain high blood levels.

CONCLUSIONS

1. In a series of 22 cases of mixed infections of the upper respiratory tract and the ear, the nose and the throat in children, we found that when treatment was with the buffered penicillin tablet, regardless of meals ("around the clock"), the blood levels were poor and the clinical results disappointing.

2. Because of pronounced individual variation in absorption, caution should be exercised in the oral use of penicillin in severe infections.

3. Overdosage rather than underdosage is the safe procedure to avoid the occurrence of penicillin-resistant organisms.

4. When nursing care is available, the intramuscular route is the route of choice for the administration of penicillin.

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16. Feinberg, S. M.: Penicillin Allergy: On Probability of Allergic Reactions in Fungus Sensitive Individuals; Preliminary Experiments, J. Allergy **15**:271 (July) 1944.

17. Penicillin Resistance, Current Comment, J. A. M. A. **127**:714 (March 24) 1945.

18. Gallardo, E.: Sensitivity of Bacteria from Infected Wounds to Penicillin: Results in One Hundred and Twelve Cases, War Med. **7**:100 (Feb.) 1945. Footnote 15*b*.

5. The buffer added to penicillin has not solved the problem of oral administration. There is need for additional knowledge about the absorption of penicillin from the gastrointestinal tract.

PART II.

A. INTRODUCTION

The poor results which we obtained in our study of buffered penicillin given orally prompted us to make additional studies on the absorption of penicillin toward the better administration in its relationship to meals and its effect on blood levels.

We initiated a series of two sets of control studies (charts 1 and 2). Seven normal adults were given 100,000 Oxford units of penicillin every hour for seven doses starting at 10 a. m. and ending at 4 p. m. Six had no breakfast, while the seventh control ate at 9 a. m. There was no food otherwise between 9 a. m. and 12:30 p. m. and none between lunch and 4 p. m. All ate the same lunch at 12:30 p. m.

Marked individual variation is seen in hourly blood levels taken (chart 1). However, the same pattern of results is seen. The method used for blood assay is the dilution method of Rammelkamp [19] in which we used our own organism, a beta hemolytic streptococcus (Pilth). Three of these normal adults (subjects 1, 2 and 4) were given ordinary penicillin in pure form dissolved in saline solution.[20] The others were given penicillin in tablet form combined with a buffer compound of aluminum hydroxide, calcium carbonate and magnesium oxide. The two best results, from the viewpoint of blood levels, are in those subjects given pure penicillin without any buffer. The 6 subjects (subjects 1 to 6 inclusive) who started on an empty stomach all showed a similar curve of blood penicillin levels. There was uniformly good absorption on an empty stomach, and poor absorption, even with hourly doses of 100,000 Oxford units, when the subject had breakfast at 9 and lunch at 12:30. Poor absorption was seen in all cases except case 4 for at least two hours after a moderate-sized luncheon. Other subjects were tried as controls with lower dosage. It was found that 100,000 Oxford units was the lowest oral dose which would regularly give a reliable blood level above 0.03 Oxford unit per cubic centimeter of blood, when given on an empty stomach. We did not consider levels below this effective.

We then tried pediatric patients as controls, using children convalescent from scarlet fever (chart 2). They were given both a buffered product of penicillin and ordinary penicillin powder dissolved

19. Foster, J. W., and Woodruff, H. B.: Microbiological Aspects of Penicillin: VI. Procedure for the Cup Assay for Penicillin, J. Bact. **47**:43 (Jan.) 1944.

20. McDermott, W., and others: Oral Penicillin, Science **101**:228 (March 2) 1945. Bunn and others.[11]

in saline solution. The penicillin was given in one dose of 50,000 or 100,000 Oxford units and was given at various times in relation to a standard, identical meal given at 11 a. m. each day. When given before this standard meal, it was then taken on an empty stomach.

This standard luncheon was a meal which was predominantly carbohydrate, consisting of one slice of bread (no butter), a small glass of artificial fruit juice, a small portion of mashed potatoes, a glass of milk

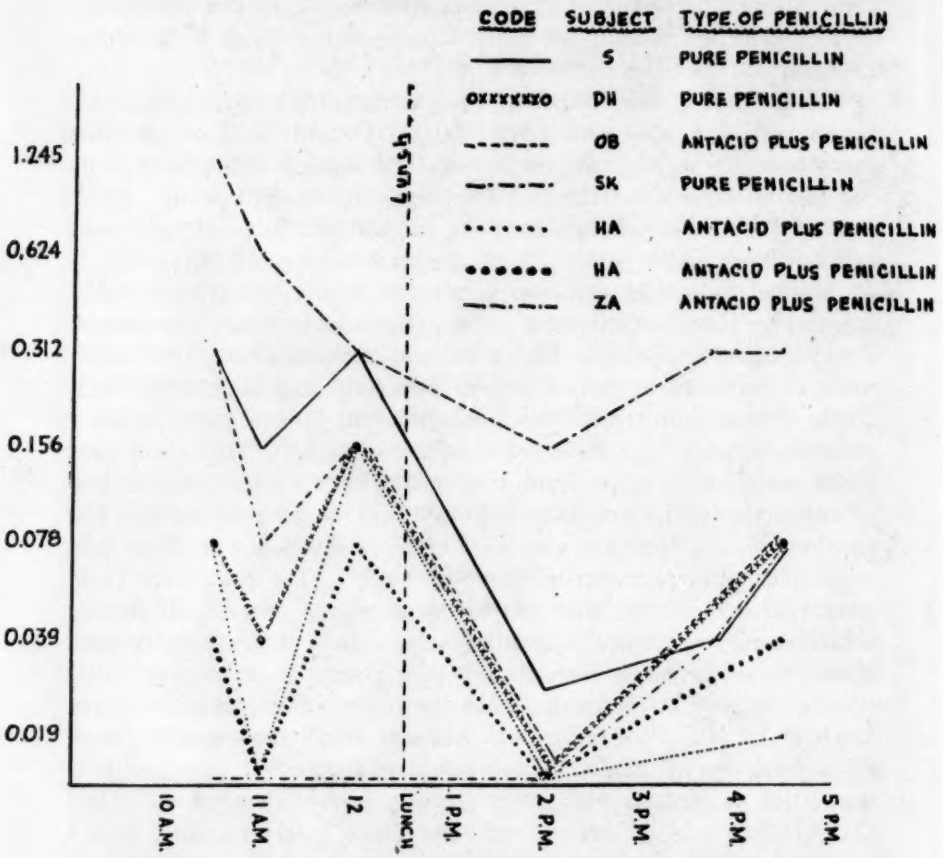

Chart 1.—Levels of penicillin in the blood of 7 control subjects given 100,000 Oxford units every hour for seven hours (10 a. m. through 4 p. m.). Levels were taken at 10:30 a. m., 11 a. m., 12 m., 2 p. m., 3:45 p. m. and 4:30 p. m. All the subjects ate the same meal at 12:30 p. m. Poor blood levels are seen after lunch despite ingestion of penicillin every hour. Subjects 1, 2, 3, 4, 5 and 6 showed good initial levels; they had no breakfast. Subject 7 had breakfast at 9 a. m., and he showed no level demonstrable until 3:45 p. m. No advantage is apparent here for use of antacid over use of pure penicillin orally.

and a small portion of pudding with flavoring. The fats and proteins (except those in milk) were limited. We calculated that a meal such as this (on an average, and not considering psychogenic factors which

vary with each person) should be out of the stomach within two to two and one-half hours.[14] This, however, is a variable figure.

At first we tried 50,000 Oxford units, but later we decided that 100,000 Oxford units produced more effective and more reliable blood

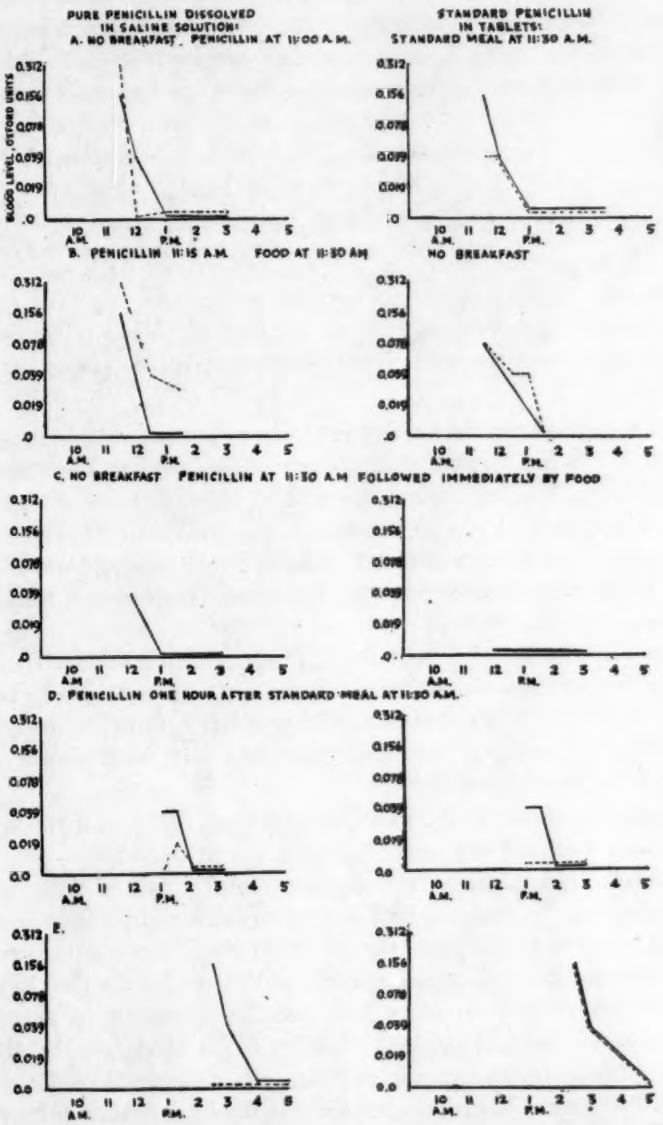
PURE PENICILLIN DISSOLVED IN SALINE SOLUTION
A. NO BREAKFAST. PENICILLIN AT 11:00 A.M.
STANDARD PENICILLIN IN TABLETS
STANDARD MEAL AT 11:30 A.M.
BLOOD LEVEL, OXFORD UNITS
0.312
0.156
0.078
0.039
0.019
.0
10 11 12 1 2 3 4 5
A.M. P.M.
B. PENICILLIN 11:15 A.M. FOOD AT 11:30 A.M.
NO BREAKFAST
C. NO BREAKFAST PENICILLIN AT 11:30 A.M. FOLLOWED IMMEDIATELY BY FOOD
D. PENICILLIN ONE HOUR AFTER STANDARD MEAL AT 11:30 A.M.
E.

Chart 2.—Levels of penicillin in the blood after one oral dose of 100,000 Oxford units taken in various time relations to a standard meal. The following results may be noted: 1. Results with unbuffered, pure penicillin are as good as with buffered product. 2. Levels are best when penicillin has been given orally thirty minutes before meal (A) or three hours after meal (E). 3. Levels do not usually persist longer than one and one-half to two hours.

levels. The purpose of this experiment was to determine the effect of stomach contents such as food on absorption of penicillin. We wished to gage just how to give our oral dosage most effectively. We also compared, under identical circumstances, the pure penicillin powder dissolved in isotonic solution of sodium chloride (usually used for parenteral treatment) to a buffered oral preparation (containing aluminum hydroxide, calcium carbonate, and magnesium oxide) in tablet form. This last was the same product which we had used in our case studies.

B. INTERPRETATION OF CHART TWO

The results of these investigations are shown on chart 2 and are sufficiently impressive to warrant a number of conclusions.

1. There appears to be no marked difference, from our controls, between the "oral" commercial product with buffer and the ordinary pure penicillin dissolved in isotonic solution of sodium chloride given orally, except that the unbuffered preparation gives somewhat better absorption.

2. The food-timing factor appears to be important with both preparations used. When penicillin was given orally one-half hour or fifteen minutes before (series A and B) and at least three hours after our standard luncheon (E) good absorption was obtained. If penicillin was given orally between these limits most of it was *not* absorbed (series C and D). Regardless of why this happened, the penicillin blood levels were below the effective levels.

Best and Taylor [14b] stated that "fluids and semi-fluids commence to leave the stomach almost immediately on being swallowed" in small jets of fluid which are constantly being forced through the pylorus. The tablet preparations lack this advantage and may remain behind to mix with the ingested food.

3. Effective blood levels, which ranged from 0.039 to 0.312 unit per cubic centimeter, did not remain after one and one-half to two hours. These levels did not reach their maximum until fifteen to thirty minutes after ingestion. We also found in a comparative study that penicillin given to children of the same size, 20,000 Oxford units intramuscularly every three hours, gave average levels of 0.03 to 1.3 Oxford units per cubic centimeter and remained demonstrable only one to two hours.

In view of the findings that effective blood levels can be obtained on oral administration, we are making certain suggestions for its use. 1. Penicillin should be given when there is the least chance of its mixing with stomach food content. 2. It should preferably be given in fluid state. 3. It could be given without any buffer. 4. It should be given in doses of 100,000 Oxford units, which is about five times the average intramuscular dose. Our findings seem to agree with Finland [3a] and

McDermott [20] and their co-workers, rather than with György [4d] and Burke [4c] and Charney,[4a] who believe the buffer to be important.

CONCLUSIONS

Reliable effective blood levels were obtained only with dosage of 100,000 Oxford units every three or four hours on an empty stomach in both children and adults.

The food-dosage-time relationship is important (regardless of any buffer) in that the feedings *must* be so arranged that the stomach is empty of food at the time of dosage with penicillin. The dosage should be, roughly, five times that of intramuscular preparations.

Similar results were obtained when pure powdered penicillin was dissolved in saline solution and given in liquid form orally as when a special "oral" preparation in tablet form with added "protective" buffers was given. In fact, the fluid preparations showed evidence of being absorbed faster, and higher blood levels were obtained.

Dr. Alfred Angrist, Director of the Department of Pathology, Queens General Hospital, gave invaluable advice and kind cooperation. The various members of the Department of Bacteriology and the nursing staff of Queens General Hospital and the Queensboro Contagious Pavilion furnished help without which this paper would not have been possible. Members of the house staff and the Social Service Department acted as volunteer controls.

1150 Grand Concourse, Bronx, N. Y. (Dr. Goldfarb).

8803 One Hundred and Forty-Sixth Street, Jamaica, N. Y. (Dr. Reisman).

SYNDROMES OF KEROSENE POISONING IN CHILDREN

MATTHEW M. STEINER, M.D.
CHICAGO

VARIOUS syndromes of kerosene poisoning in children have been described in the literature with relatively few fatalities as a result of accidental ingestion of kerosene.[1] In general, the clinical picture is one of acute intoxication with evidence of cerebral depression, particularly of the vagus and respiratory centers; most of these patients recover in a few days with little or no treatment. However, in a large number of children who ingest kerosene changes develop in the lungs [1g]; these are detected clinically or roentgenographically, and vary from slight "infiltrations" to more serious complications.[2] In addition, the frequent aspiration of kerosene or kerosene-containing gastric contents plays a role not only in the development of extensive pulmonary damage but also in the production of degenerative changes in other organs.

The purpose of this clinical study is to analyze 35 cases of accidental kerosene poisoning in children from two geographic areas having different sources of kerosene, namely, Chicago and Oceanside, Calif.[3] An attempt will be made to evaluate the factors involved in the production of various syndromes of kerosene poisoning, which have been

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From the Children's Memorial Hospital.

1. (*a*) Barbour, O.: Kerosene Poisoning, J. A. M. A. **87**:488 (Aug. 14) 1926. (*b*) Price, J. P.: Kerosene Poisoning in Children, ibid. **99**:214 (July 16) 1932. (*c*) Higgins, J. M.: Rapidly Fatal Result in Child from Ingestion of Kerosene, Pennsylvania M. J. **36**:526 (April) 1933. (*d*) Waring, J. I.: Pneumonia in Kerosene Poisoning, Am. J. M. Sc. **185**:325 (March) 1933. (*e*) Farabaugh, C. L.: Kerosene Poisoning, Minnesota Med. **19**:780 (Dec.) 1936. (*f*) Nunn, J. A., and Martin, F. M.: Gasoline and Kerosene Poisoning in Children, J. A. M. A. **103**:472 (Aug. 18) 1934. (*g*) Lesser, L. I.; Weens, H. S., and McKey, J. B.: Pulmonary Manifestations Following Ingestion of Kerosene, J. Pediat. **23**:352 (Sept.) 1943. (*h*) Lowery, O. W.: Kerosene Poisoning, Texas State J. Med. **41**:259 (Sept.) 1945.

2. (*a*) Price.[1b] (*b*) Scott, E. P.: Ingestion of Kerosene Complicated by Pneumonia, Pneumothorax, Pneumopericardium and Subcutaneous Emphysema: J. Pediat. **25**:31 (July) 1944. (*c*) Lavenstein, A. F.: Kerosene Intoxication, ibid. **26**:395 (April) 1945.

3. The patients in groups II and III were treated by the author while stationed at the Outpatient Department, United States Naval Hospital, Santa Margarita Ranch, Oceanside, Calif.

segregated on the basis of severity and complications into three main groups: (1) acute toxicity and depression of the central nervous system with minimal pulmonary changes and with rapid recovery; (2) severe pneumonia, hyperpyrexia and prolonged recovery, and (3) severe pneumonia with evidence of degenerative changes in the myocardium, the liver, the kidney and the gastrointestinal tract.

CLINICAL STUDY

GROUP I.—*Acute Toxicity and Depression of Central Nervous System with Minimal Pulmonary Changes and Rapid Uneventful Recovery* (table 1).—There were 26 patients in this group; the ages ranged from 13 to 31 months, and the patients were seen one to sixteen hours after the accidental ingestion of kerosene. Vomiting and choking occurred in almost all patients; drowsiness developed in 10 of them, and it is noteworthy that this took place in some who were seen within an hour after the accident. Tachycardia and tachypnea were encountered frequently, and there were 6 patients with cyanosis as early as two hours after the accident. There were 18 patients in whom no abnormalities were noted in the chest on admission; of these, 8 showed "infiltrations" on roentgen examination; roentgenograms of the chest for 2 patients showed no abnormality, and 8 were not checked roentgenologically. The low grade fever which was seen in 7 patients did not last more than two days. The emergency treatment consisted of gastric lavage with weak sodium bicarbonate solution; in some cases nikethamide and caffeine, alone or combined, were employed because of the severity of the initial findings. In this group, the presenting picture of the child at the time of admission was out of all proportion to the benign prognosis and the subsequent clinical course in the hospital. Most of the patients recovered within twenty-four to forty-eight hours and were ready to go home in three to four days. Except for a transient leukocytosis, the laboratory observations were not unusual; in 1 instance there developed on the second day loose stools, which contained occult blood.

CASE 1.—R. T., a white boy aged 13 months, was seen three hours after ingesting an unknown amount of kerosene. On the way to the hospital he vomited and coughed repeatedly. On admission, he appeared limp and drowsy. Gastric lavage with weak sodium bicarbonate solution yielded a moderate amount of gastric contents having a strong kerosene odor. The temperature was 98.6 F.; the pulse was thready and had a rate of 150 per minute; the respirations were shallow and at the rate of 48 per minute. The mouth and pharynx appeared "burned." No abnormalities were noted in the chest, and no other abnormalities were noted on examination. A roentgenogram of the chest revealed mottled densities in the right cardiohepatic angle.

He received ½ ampule each of nikethamide (0.75 cc. of 25 per cent solution) and caffeine (0.5 Gm.) on admission. Within six hours he was able to take fluids by mouth and appeared more alert; there was no vomiting only occasional coughing.

TABLE 1.—*Group I; Acute Toxicity and Depression of the Central Nervous System with Minimal Pulmonary Changes and Rapid Uneventful Recovery*

Case No.	Age (Mo.)	Sex	Hours After Ingestion	History	Signs and Symptoms	Roentgenogram	Treatment	Laboratory Data
1	13	M	3	Cough, vomit, limp	Cyanosis, tachypnea, normal chest, fever 1 day	Patchy mottling both bases	Gastric lavage, caffeine, nikethamide	Not unusual
2	14	F	4	Cough, vomit, drowsy	Tachypnea, normal chest, fever 2 days	Chest normal	Gastric lavage	Not unusual
3	14	F	2	Cough, vomit, drowsy	Cyanosis, feeble pulse, tachypnea, normal chest, fever 2 days	None taken	Gastric lavage, caffeine	Not unusual
4	14	F	1	Cough, vomit, drowsy and then stuporous	Tachypnea, normal chest, fever 2 days, drowsy into stupor	None taken	Gastric lavage, caffeine, nikethamide	Not unusual
5	15	M	2	Cough, vomit, drowsy	Cyanosis, tremor, rales at base of right lung, fever 1 day	Patchy mottling, base of right lung	Gastric lavage, nikethamide, caffeine	Not unusual
6	15	F	3	Cough, vomit, drowsy	Tachypnea, drowsy, normal chest, fever 2 days	Normal chest	Gastric lavage, caffeine	Not unusual
7	16	F	4	Cough, vomit, limp, stupor	Cyanosis, tachypnea, drowsy to stupor, normal chest, fever 2 days	Patchy mottling, base of right lung	Gastric lavage, caffeine, nikethamide	Not unusual
8	16	M	2	Vomit, stupor, cyanosis	Cyanosis, stupor, normal chest, fever 1 day	None taken	Gastric lavage, caffeine	Not unusual
9	16	F	3	Cough, vomit, drowsy	Feeble pulse, tachypnea, normal chest, fever 1 day	Patchy mottling, bases of both lungs	Gastric lavage, caffeine	Not unusual
10	17	M	1	Cough, drowsy, tremors	Cyanosis, feeble pulse, tachypnea, rales at base of right lung, fever 1 day	Patchy mottling, base of right lung	Gastric lavage, caffeine, nikethamide	Not unusual
11	17	M	1	Cough, vomit	Normal chest, afebrile	None taken	Gastric lavage	Not unusual
12	18	F	3	Cough, vomit, cyanosis	Cyanosis, grunt, tachypnea, drowsy, normal chest, fever	Patchy mottling, bases of both lungs	Gastric lavage, nikethamide	Occult blood in stool
13	18	M	4	Cough, vomit	Normal chest, afebrile	Normal chest	Gastric lavage	Not unusual
14	19	M	2	Cough, vomit, drowsy	Drowsy, cough, tachypnea, normal chest, afebrile	Patchy mottling lower lobe right lung	Gastric lavage, caffeine	Not unusual
15	19	F	12	Cough, vomit, anorexia	Normal chest, afebrile	Patchy mottling, base of right lung	Gastric lavage	Not unusual
16	20	F	4	Vomit, drowsy, limp	Drowsy, cyanosis, normal chest, fever 2 days	Normal chest	Gastric lavage, nikethamide, caffeine	Not unusual
17	21	F	1	Cough, drowsy	Normal chest, irritability, fever	Not done	Gastric lavage	Not unusual
18	21	M	10	Vomit, drowsy, labored breathing	Tachypnea, fever 2 days, rales base of right lung	Mottled density base of right lung	Gastric lavage, penicillin, fluids subcutaneously	Not unusual
19	22	F	6	Cough, vomit, drowsy	Rales at bases of both lungs, afebrile irritable	Mottled density bases of both lungs	Gastric lavage, penicillin	Not unusual
20	23	F	1	Cough, listless, labored breathing	Drowsy, tachypnea, normal chest, fever 1 day	Not done	Gastric lavage	Not unusual
21	23	M	1	Vomit, stupor, cyanosis	Cyanosis, rales at base of right lung, fever 2 days	Mottled densities bases of both lungs	Gastric lavage	Not unusual
22	23	F	2	Cough, vomit, drowsy	Drowsy, normal chest, afebrile	Not done	Gastric lavage	Not unusual
23	24	M	2	Cough, vomit, drowsy	Tremors, normal chest, afebrile	Not done	Gastric lavage	Not unusual
24	28	F	16	Cough, vomit, cyanosis	Drowsy, cyanosis, normal chest, afebrile	Mottled densities base of right lung	Gastric lavage, nikethamide, caffeine	Not unusual
25	29	F	2	Cough, vomit, drowsy	Normal chest, afebrile	Normal chest, afebrile	Gastric lavage	Not unusual
26	31	M	1	Cough, vomit	Drowsy, rales at base of right lung, fever 2 days	Mottled density base of right lung	Gastric lavage	Not unusual

The temperature remained normal, the pulse was stronger and the respiration rate was 40 per minute. Examination of the urine disclosed no abnormality. He was discharged improved on the fifth day. A roentgenogram of the chest showed that the mottled densities had largely disappeared.

GROUP II.—*Severe Pneumonia, Hyperpyrexia and Prolonged Recovery* (table 2).—There were 6 patients in this group; the ages ranged from 17 to 20 months, and they were seen one to eighteen hours after the accidental ingestion of the kerosene. Although the infants were subjected to attacks of vomiting and coughing as in the preceding group, they all appeared more acutely ill on admission; all but 1 were either stuporous or comatose. The examinations disclosed a fairly uniform picture of cyanosis, tachypnea, feeble rapid pulse and high temperature; in 2 patients tremors of the extremities were noted. In all these patients rales were heard in the chest at one or both bases, and roentgen examination disclosed patchy mottling, which became confluent during the hospitalization; in 3 cases fluid developed in the chest. Thoracentesis was not employed, since the fluid was minimal and penicillin was employed early and in relatively large doses. The emergency treatment consisted of gastric lavage with weak sodium bicarbonate solution, nikethamide and caffeine. Penicillin was employed in large doses and continued until the condition of the patient was definitely improved. In view of the danger of pulmonary edema,[4] hypertonic solution of dextrose was employed in addition to other fluids given parenterally. These patients remained stuporous for thirty-six to forty-eight hours, and even after regaining consciousness they resisted oral feedings or medications. The laboratory data disclosed transient leukocytosis, normal urine and, in 2 cases, occult blood in the stools.

CASE 2.—A. K., a white boy aged 17 months, was seen one hour after ingesting an unknown amount of kerosene. On the way to the hospital he vomited and coughed repeatedly, and on admission he was comatose. Gastric lavage with weak sodium bicarbonate solution yielded a large amount of gastric contents having a strong kerosene odor. Within an hour after examination the temperature rose to 103 F.; cyanosis became pronounced, and grunting respirations with dilatation of the alae nasi developed. The pulse was thready and at the rate of 160 per minute. Over the right side of the chest posteriorly there were dulness, diminished breath sounds and fine crepitant rales. A roentgenogram of the chest (four hours after the accident) revealed patchy infiltration in the mesial aspect of the lower third of the right lung and adjoining the apex of the heart in the left lung. The white blood cell count showed 12,000 cells, and the urine was within normal limits.

He received an ampule each of nikethamide and caffeine. Penicillin, hypertonic solution of dextrose and other fluids were administered parenterally, and he was placed in an oxygen tent. On the third day his condition was critical; the respirations were labored, cyanosis was pronounced and he was delirious, with tem-

4. Lesser and others.[1g] Scott.[2b]

TABLE 2.—*Group II; Severe Pneumonia, Hyperpyrexia and Prolonged Recovery*

Case No.	Age (Mo.)	Sex	Hours After Ingestion	History	Signs and Symptoms	Roentgenogram	Treatment	Laboratory Data
27	17	M	1	Cough, vomit, coma	Cyanosis, tachypnea, temperature 103 F., rapid pulse, grunt, rales at base of right lung	Patchy mottling base of right lung, later consolidation and spread to upper lobe of left lung	Gastric lavage; penicillin, nikethamide and caffeine; fluids intravenously	Leukocytosis; normal urine
28	18	F	18	Cough, vomit, grunt, dysphagia, labored breathing, stupor	Cyanosis, dyspnea, temperature 102 F., grunt, normal chest, irritable	Density in lobe of right lung with fluid	Caffeine, fluids subcutaneously; acetylsalicylic acid	Normal urine
29	18	M	2	Cough, vomit, stupor	Cyanosis, grunt, feeble pulse, temperature 102 F., rales at base of right lung	Patchy mottling base of right lung, spread to bases and upper lobes of both lungs, fluid at base of right lung	Gastric lavage; penicillin; hypertonic solutions; fluids intravenously; nikethamide and caffeine	Leukocytosis; normal urine
30	19	F	3	Cough, vomit, tremors, coma	Cyanosis, grunt, tachypnea, tremors, feeble pulse, temperature 103 F., rales at bases of both lungs	Patchy mottling bases of both lungs; later, consolidation of right lung	Gastric lavage; nikethamide and caffeine; penicillin; hypertonic solution; fluids intravenously	Leukocytosis; urine normal; occult blood in stool
31	20	F	3	Cough, vomit, cyanosis, stupor	Cyanosis, grunt, temperature 102 F., feeble pulse, rales base of right lung	Mottled density base of right lung; later, consolidation with fluid	Gastric lavage; nikethamide and caffeine; penicillin; hypertonic solution; fluids intravenously	Leukocytosis; urine normal

perature ranging from 103 to 106 F. There was a larger area of dulness to flatness over the lower lobe of the right lung with diminished to absent breath sounds, and there were signs of pneumonia over the upper lobe of the left lung. On the seventh day of penicillin therapy, after a total amount of 500,000 units had been administered, there developed a diffuse macular eruption on the chest, which faded in three days without residual pigmentation. Twelve days after admission his condition was improved, although the temperature ranged between 100 and 101 F. The signs in the chest were limited to dulness and diminished breath sounds over the right lung posteriorly. He was now taking fluids by mouth, and his subsequent course until discharge on the twenty-third day was uneventful. The urine on repeated examination was within normal limits. A roentgenogram of the chest on discharge showed no infiltration of the pulmonary fields.

GROUP III.—*Severe Pneumonia with Evidence of Degenerative Changes in Myocardium, Liver, Kidney and Gastrointestinal Tract* (table 3).—There were 4 patients in this group; the ages ranged from 16 to 26 months, and they were seen three to six hours after the accidental ingestion of kerosene. The general appearance of these patients was the same as in group II; they were acutely ill and either stuporous or comatose. There were rales and diminished breath sounds over the bases of one or both lungs, and roentgenographic examination confirmed the presence of pulmonary changes. The subsequent development of confluent pneumonia was rapid and severe with fluid in the chest in 2 of the patients. Evidence of cardiac dilatation was obtained on serial roentgenograms in 3 patients; hepatosplenomegaly occurred in all during the course of the disease but disappeared before the patients left the hospital. In case 34, auricular fibrillation and flutter was associated with cardiac failure, and digitalis was employed, with good effect. It is noteworthy that all these patients showed persistent urinary changes consisting of albumin, cells and casts; again, these changes were reversible. In 3 patients, the stools showed occult blood and in case 34, reported here, vomiting of coffee ground material ensued repeatedly.

CASE 3.—P. V., a white boy aged 26 months, was seen four hours after ingesting an unknown amount of kerosene. On the way to the hospital he vomited and coughed repeatedly. On admission he was stuporous and deeply cyanotic; the temperature was 102.2 F., the pulse was thin and at the rate of 120 per minute and the respirations were shallow, abdominal and at the rate of 80 per minute! Gastric lavage with weak sodium bicarbonate solution yielded a moderate amount of gastric contents having a strong kerosene odor. Over the upper part of the right axilla there were dulness and diminished breath tones, and coarse moist rales were heard over the bases of both lungs. The heart sounds were heard poorly, and the liver was palpable 1 fingerbreadth below the costal margin. The superficial reflexes were depressed.

He received an ampule each of nikethamide and caffeine and was placed in an oxygen tent. Penicillin, hypertonic solution of dextrose and other fluids were administered (fig. 1). Six hours later there was dulness over the whole right side of the chest with flatness and absence of breath sounds at the base suggestive of fluid (fig. 2). An examination of the urine disclosed no abnormality. The following

TABLE 3.—*Group III; Severe Pneumonia with Evidence of Degenerative Changes in Myocardium, Liver, Kidney and Gastrointestinal Tract*

Case No.	Age (Mo.)	Sex	Hours After Ingestion	History	Signs and Symptoms	Roentgenogram	Treatment	Laboratory Data
32	16	M	3	Cough, vomit, coma	Cyanosis, shallow respirations, feeble pulse, tremors, rales at bases of both lungs, temperature 102 F., hepatosplenomegaly	Patchy mottling at bases of both lungs; later, consolidation with fluid; enlarged cardiac shadow	Gastric lavage; niketh-amide and caffeine; penicillin; hypertonic solution; fluids intravenously	Urine; albumin, casts, cells; occult blood in stool
33	20	F	6	Cough, vomit, stupor	Cyanosis, tremors, shallow respirations, rales in bases of both lungs; fluid in right side of chest; prolonged fever; hepatosplenomegaly	Patchy mottling base of right lung; later, consolidation and fluid; cardiac enlargement	Gastric lavage; niketh-amide and caffeine; penicillin; hypertonic solution; fluids intravenously	Albumin and casts; marked leukocytosis
34	26	M	4	Cough, vomit, stupor	Cyanosis; labored breathing; feeble pulse; tracheal rales; rales at bases of both lungs; later consolidation and fluid in right side of chest; hepatosplenomegaly; temperature 102 F. prolonged; coffee ground vomitus and heart failure; auricular fibrillation (EKG)	Patchy mottling right side of chest and spread with fluid; cardiac enlargement	Gastric lavage; niketh-amide and caffeine; penicillin; hypertonic solution; fluids intravenously; 'digalen" intramuscularly	Albumin and casts; leukocytosis; occult blood in stool
35	28	F	6	Cough, vomit, stupor	Cyanosis; tachypnea; feeble pulse; rales in base of right lung; temperature 103 F. prolonged; hepatosplenomegaly	Patchy mottling base of right lung with fluid; later consolidation	Gastric lavage; niketh-amide and caffeine; penicillin; hypertonic solution; fluids intravenously	Albumin and casts; leukocytosis; occult blood in stool

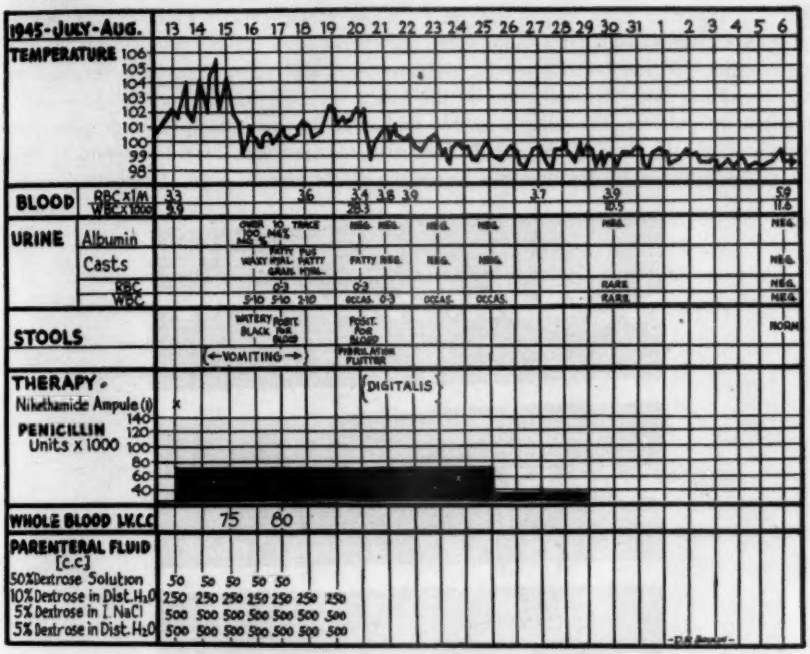

Fig. 1.—Temperature, laboratory data and therapy in case 34.

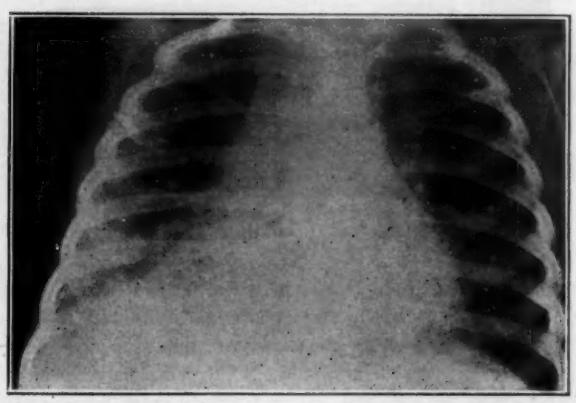

Fig. 2.—Roentgenogram taken ten hours after ingestion of kerosene. Mottled densities and fluid may be seen at base of right lung.

day his condition appeared critical, with hyperpyrexia, delirium and markedly labored respirations. Two days later the urine contained 100 mg. of albumin, many waxy and fatty casts and many white blood cells. Vomiting of coffee ground material occurred at intervals, and there were jerking movements of the extremities. Watery black stools were passed which gave a positive reaction to the benzidine test. Examination of the heart revealed barely audible tones with marked irregularity, the pulse was thin and irregular and the cardiac dulness was increased to the left of the nipple line and to the right of the sternum. The liver was palpable 3 fingerbreadths below the costal margin. An electrocardiogram

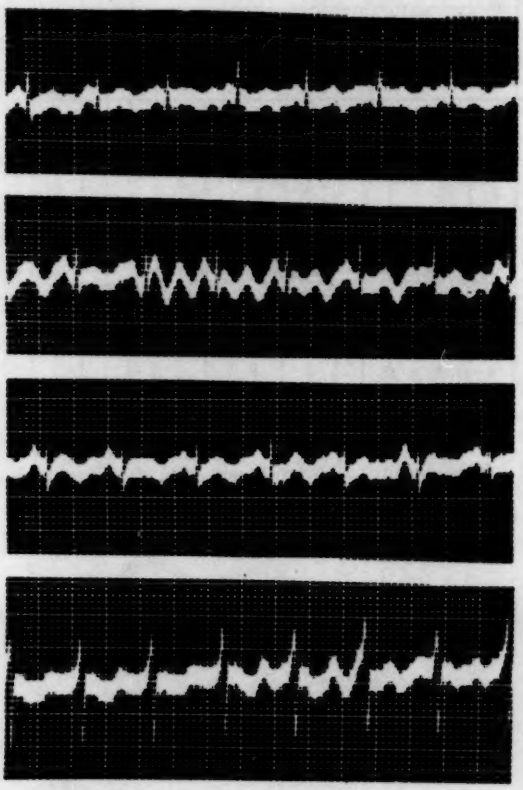

Fig. 3.—Auricular fibrillation and flutter.

showed evidence of myocardial damage as indicated by depressed S-T intervals and inverted T waves. Changes in rhythm in one place showed the relatively low waves of fibrillation and in another the saw-tooth appearance of flutter (fig. 3). Following digitalization with "digalen" N. N. R. administered intramuscularly, there was notable improvement, and an electrocardiogram taken four days later showed considerable reversal with sinus rhythm.

During the following week, the urine continued to show albumin, casts and cells. Over the lower lobes of both lungs dulness and diminished breath sounds persisted, with scattered moist rales and evidence of fluid at the base of the right lung. Ten days later he appeared much improved; he was out of the oxygen tent and was

taking fluids orally. The urine gradually became normal; cardiac dulness diminished and the rhythm was regular. However, the abnormalities in the chest persisted, and a roentgenogram revealed residual fluid or thickened pleura at the base of the right lung. At discharge, after twenty-six days of hospitalization, there were minimal findings over the right side of the chest posteriorly attributable to a thickened pleura. The urine was normal and an electrocardiogram showed no abnormalities.

COMMENT

The central nervous system of infants is strikingly sensitive to kerosene, and absorption from the stomach is proabably rapid enough to produce changes within an hour after an accident. Whereas rapid feeble pulse, shallow respirations, cyanosis and drowsiness and occasional muscular twitchings at the time of admission may appear ominous in such infants, most of the patients in group I were out of "danger" in a few hours. Even in this group, the lungs were involved so frequently that either most of these patients aspirated varying amounts of kerosene early or else the changes resulted from gastric absorption via the blood stream. The patients in group II differed from those in group I in that they appeared more acutely ill on admission, the cerebral toxicity persisted longer, stupor or coma was apparent, the fever was intense and prolonged and the changes in the lungs rapidly progressed from a patchy mottling to confluent pneumonia with minimal amounts of fluid in the chest. The aspiration of kerosene into the lungs with subsequent pulmonary damage accounted for the stormy clinical picture in this group; moreover, the effect on the central nervous system was augmented by the increased absorption of the kerosene by the expansive pulmonary circulation. In the patients in group III, there were superimposed on the toxicity and pneumonia the degenerative effects of absorbed kerosene on liver, spleen, kidney and myocardium. In the case reported the myocardial involvement was severe enough to produce auricular fibrillation and flutter; this has not been previously encountered in the literature after the ingestion of kerosene. Such degenerative changes in the tissues, regardless of their severity, have, fortunately, been reversible in my experience.

The part played by absorption and/or aspiration in the production of various syndromes will be discussed in connection with experimental investigations. Clinically it appears that absorption from the stomach has enough potentiality for pathologic effect to warrant the prompt removal of kerosene from the stomach by gastric lavage. Yet, while such removal has been advocated in the emergency treatment, the development of gastric hyperemia and occasional multiple erosions of the gastric mucosa [1h] should make one exercise proper caution during this procedure. Since it is difficult to prognosticate the changes in the lungs, I have employed penicillin early and in doses sufficient to suppress the secondary infection which invariably takes place after the

vascular and parenchymal damage to the lungs. That pulmonary edema also occurs early has been demonstrated in experimental animals,[4] and this probably plays a definite role in the early fatalities from ingestion and aspiration of kerosene. Hence I have employed repeated administration of hypertonic dextrose solutions together with the oxygen tent in the early treatment of the acutely ill patient. Many of the infants have refused fluids and food for days after admission, and it is essential to maintain adequate fluid and electrolyte requirements parenterally.[1] Blood transfusions have been used when indicated.

It is difficult to evaluate the factors concerned in the production of various syndromes of kerosene poisoning. One must consider the age of the patient, the type and source of the kerosene, the amount ingested and retained, the extent of vomiting and aspiration, the nature and rapidity of the emergency treatment and the subsequent therapy. Infants are more susceptible than adults to ingested kerosene,[1e] and experiments have demonstrated that young rabbits show a greater susceptibility to kerosene even in smaller doses per kilogram.[5b] In a series of investigations on the toxicity of various types of kerosene in experimental animals, Deichmann [5b] has shown that the percentage of deaths from the same dose of kerosene varied from 0, with the highly purified kerosene, to as high as 60, with less purified types. Hence, the source of the kerosene and the extent of its purification (or its content of impurities) influence to some extent the nature of response either by absorption or by aspiration. There is no doubt that, whereas aspiration into the lungs plays a major role in the morbidity of kerosene poisoning, the kerosene ingested by the patients in group II and III [6] was among the types with the highest toxicity in Deichmann's series.

One cannot readily estimate the amount of kerosene retained or aspirated by these patients; it seems to follow that the greater the involvement of the lungs, via absorption and aspiration, the greater the extent of the toxicity and the morbidity. The potentialities for pathologic change in the younger patient as a result of ingesting kerosene are enhanced by the frequency of vomiting and aspiration of kerosene into the lungs. The nature of kerosene itself, particularly its low volatility, makes it likely that irritation of tissues will be inevitable, since it does not pass readily, if at all, from the lungs in the expired air. Hence, pulmonary complications have been the subject of much discussion because of the frequency of clinical and roentgenologic evidence of pneumonia.[7]

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5. (*a*) Lesser and others.[1g] (*b*) Deichmann, W. E.; Kitzmiller, K. V.; Witherup, S., and Johansmann, R.: Pneumonia, Pneumothorax and Emphysema Following Ingestion of Kerosene, Ann. Int. Med. **21**:803 (Nov.) 1944.

6. This refers to the sources of kerosene in the Oceanside, Calif., area.

7. Waring.[1d] Lesser and others.[1g] Scott.[2b]

In the pathogenesis of this pneumonia, the role played by aspiration alone or by absorption from the gastrointestinal tract together with aspiration has been dealt with by numerous investigations. Waring's [1d] experiments with dogs suggested that the mode of action consisted of aspiration of kerosene directly into the lungs or by regurgitation from the stomach into the lungs. Nunn and Martin [1f] commented on the difference in patients who only ingested kerosene and those who both ingested and aspirated it into the lungs. Lesser, Weens and McKey [1g] concluded from experimental work on rabbits, who do not vomit, that pulmonary manifestations in these animals are due to aspiration of kerosene into the lungs rather than to absorption from the gastrointestinal tract. Rabbits were given varying amounts of kerosene by stomach tube, and no changes were noted in the lungs; however, when the kerosene was administered via tracheal catheter there developed pulmonary edema and later confluent pneumonia.

Recently, the pathogenesis of kerosene pneumonia and the mode of action of kerosene following accidental ingestion have been reviewed by Deichmann and others.[5b] They repeated oral administration of kerosene to rabbits and also administered lethal doses of kerosene intraperitoneally and studied the changes in the lungs and other organs. They concluded that vascular damage via absorption through the blood stream accounted for the changes in the bronchi and lungs, and the pathologic changes in the lungs were of the same general character whether the administration of the kerosene was by stomach tube or by intraperitoneal injection. In view of the changes in the lungs from the kerosene carried via the blood stream, as well as from direct contact resulting from aspiration, these investigators stressed the early and efficient removal of all traces of kerosene from the gastrointestinal tract in the emergency treatment of kerosene poisoning.

Moreover, the changes in liver, spleen, kidney and myocardium which I have experienced in the more seriously ill patients have also been attributed to vascular damage from absorption. In my experience these alterations have not led to any permanent damage. One should be on the lookout for such variations during the course of the disease in the seriously ill patients and adjust the therapy to aid in the restoration of normal function.

SUMMARY AND CONCLUSIONS

Syndromes of kerosene poisoning in children were segregated into three main groups on the basis of severity and complications. In group I there were 26 patients, who showed signs of acute toxicity, depression of the central nervous system, minimal pulmonary changes and rapid recovery with minimal treatment. In group II there were 6 patients, in whom severe pneumonia and hyperpyrexia developed

with prolonged recovery and convalescence. In group III there were 4 patients, in whom severe pneumonia and degenerative changes in liver, kidney, spleen and myocardium developed. A complication hitherto not encountered has been that of auricular fibrillation and flutter and is reported in detail (case 34).

Changes in the gastrointestinal tract as a result of direct contact with kerosene were evidenced by the presence of blood in the vomitus and stool in a number of cases.

The emergency treatment consisted of gastric lavage with copious amounts of weak sodium bicarbonate solution for the removal of the kerosene and the prevention of further absorption and damage to the gastrointestinal mucosa. Nikethamide and/or caffeine have been employed when such stimulants seemed indicated by the condition of the patient.

Administration of penicillin was instituted early in the cases of more serious poisoning to offset bacterial invasion of the lungs. Hypertonic (50 per cent) dextrose solution and oxygen appeared to be efficacious in diminishing the hazard of early pulmonary edema. Adequate fluids and electrolytes were maintained by parenteral administration, especially in those critically ill patients with either severe pneumonia or degenerative changes in various organs. Digitalis was employed as indicated in the report of a case.

6354 Broadway.

SECONDARY PANCREATITIS

PETER V. VÉGHELYI, M.D.
BUDAPEST, HUNGARY

IT HAS long been known that various infections may attack the pancreas, especially if neighboring organs are first affected, but hematogenous involvements also occur. Acute and chronic inflammations of this organ were registered during and after a number of diseases, such as typhoid,[1] spirochetal jaundice,[2] scarlet fever and diphtheria,[3] malaria,[4] pneumonia[5] and influenza.[6] It is, however, together with epidemic parotitis that—according to the astonishingly few investigations into this problem—such a condition seems to be most frequent. Involvement of the pancreas was seen in 85 out of 652 cases by Simonin,[7] in 5 out of 33 by Edgecombe[8] and in 9 of 40 by Sharp.[9] In spite of the complication's being mentioned in every textbook of pediatrics, the cases diagnosed throughout the world are few and the number published of those thoroughly examined remains well under 100. Yet the inflammation, once it has become irreversible and chronic, healing with scars of inactive connective tissue, must lead to a permanent decrease in pancreatic excretion. It depends on the amount of tissue left able to function whether pronounced symptoms arise or not, but in all probability not every case will remain symptomless. Why, then, are so few cases of this seemingly common condition diagnosed? I will endeavor to demonstrate the cause of this apparent contradiction.

From the Department of Pediatrics of the Hungarian Petrus Pázmány University.

1. Weber: Tr. Path. Soc. London **12**:96, 1861. Mayer, A.: Deutsche med. Wchnschr. **44**:857, 1918.

2. Carnot, P.: Maladies des glandes salivaires et du pancréas, Thesis, Paris, J. B. Baillière & fils, 1908.

3. Goldie: Lancet **2**:1295, 1912.

4. Egdahl, A.: Bull. Johns Hopkins Hosp. **18**:130, 1907.

5. Rudolph, W.: Deutsches Arch. f. klin. Med. **87**:1, 1906.

6. Hirschfeld, F.: Berl. klin. Wchnschr. **45**:537, 1908. Luccarelli, V.: Riv. med. **28**:134, 1920.

7. Simonin, J.: Semaine méd. **23**:248, 1903.

8. Edgecombe, W.: Practitioner **80**:194, 1908.

9. Sharp, J. G.: Lancet **1**:162, 1909.

The symptoms of pancreatic mumps, as those of secondary pancreatitis in general, have been variously described by different authors. (I wish to avoid the term "parotitis pancreatica" as, on the one hand, it is incorrect and, on the other, it may happen that inflammation of the pancreas may precede the swelling of the parotid gland, as in the cases of Friedjung [10] and Csapó.[11]) Most authors, including Rommel,[12] Barbieri,[13] Cheinisse,[14] Farnam [15] and Brahdy and Scheffer,[16] report cases with a sudden onset, high temperature, grave abdominal symptoms, vomiting and intense pain characteristically radiating backward, followed in some instances by jaundice and enlargement of the spleen. The pancreas may become palpable. Recovery used to occur in five to six days, but deaths are also reported.[17] Thus the descriptions reveal some acute, alarming abdominal tragedy, closely resembling and only slightly more innocent than the picture of acute necrosis. One must suppose that that is why the various investigators paid so little attention to the accompanying dysfunction of the gland, i. e., to the diminution of the incretory and excretory functions resulting in steatorrhea and azotorrhea, in acetonuria and glycosuria. Although metabolism had been investigated in several instances especially before the cause of diabetes became known, the only symptom to attract attention was the glycosuria persisting in a considerable proportion of the patients.[18] These diabetic patients gave the first proof that pancreatitis does not come to an end in a week when the acute symptoms subside, but becomes, at least in some instances, chronic. The descriptions, dealing almost exclusively with the gravest forms or with resulting diabetes, are to be blamed for the fact that the cases with a less conspicuous onset and presenting no glycosuria are rarely diagnosed and have been reported by only a few authors most familiar with the problem.[19] It is probable,

10. Friedjung, J. K.: Ztschr. f. Kinderh. **46**:303, 1928.

11. Csapó: Personal communication to the author.

12. Rommel, in von Pfaundler, M., and Schlossmann, A.: Handbuch der Kinderheilkunde, Leipzig, F. C. W. Vogel, 1931, vol. 3, p. 383.

13. Barbieri, V.: Gazz. d. osp. **30**:273, 1909.

14. Cheinisse, L.: Semaine méd. **32**:85, 1912.

15. Farnam, L. W.: Am. J. M. Sc. **163**:859, 1922.

16. Brahdy, M. B., and Scheffer, I. H.: Am. J. M. Sc. **181**:255, 1931.

17. Lereboullet, P., and Lelong, M.: Bull. et mém. Soc. méd. d. hôp. de Paris **22**:431, 1924. Lemoine, G. H.: Semaine méd. **25**:332, 1905.

18. Couronne, P.: Oreillons et diabete, Thesis, Paris, 1927. Labbé, M., and Debré, R.: Bull. et mém. Soc. méd. d. hôp. de Paris **45**:1306, 1921. Footnote 6.

19. (*a*) Neurath: Wien. med. Wchnschr. **61**:1217, 1911. (*b*) Comby: Traité de médecine des enfants, Paris, Masson & Cie, 1924. (*c*) Gross, in Gross, O., and Guleke, N.: Die Erkrankungen des Pankreas, Berlin, Julius Springer, 1924, p. 165. (*d*) Katsch, G.: Verhandl. d. Tag. ü. Verdauungs- u. Stoffwechselkr. (1924), 1925, p. 89.

however, that a decrease in the production of enzymes is more frequent than glycosuria, as the exocrine system of the gland proves invariably less resistant than the endocrine one. The dysfunctions of the former cannot be checked easily. In fact, when its consequences, like hypotrophy or, as a terminal result, the celiac syndrome, arise, the origin of the condition can seldom be detected any more, especially if the primary infection has been a light and transient one, such as influenza or mumps.

In order to elucidate these statements, 3 cases selected from extensive material will be reported.

REPORT OF CASES

CASE 1.—I. R. G., a boy of 4 years from a healthy family, had been followed closely by my colleagues and me since his birth and was developing normally until he became ill with parotitis. Only a slight bilateral swelling, light pain and almost no fever were present. He was confined to bed, but no treatment was required.

On the sixth day of his illness, when the swelling had already subsided, the temperature rose to 38 C (100.4 F.). Palpation revealed moderate tenderness above the umbilicus, and he passed several bulky, foul-smelling stools. Owing to the latter, involvement of the pancreas was suspected in spite of the absence of the classic signs like vomiting, severe spontaneous pain and palpable pancreas. Examination on the same day revealed 50 per cent unsplit fat in the dry substance of the feces, microscopically many fat globules and undigested muscle fibers. There were traces only of lipase and trypsin. Blood sugar was 90 mg. per hundred cubic centimeters, the amylase content was normal, and there were traces of sodium arsanilate–stable lipase. Diastase in the urine, incubated at 38 C. for thirty minutes, was 60 Willstätter units, or normal. On the following day the analysis of stool gave about the same results. Blood sugar was 110 mg. per hundred cubic centimeters. On the third day this rose to 155 mg., but as yet no sugar could be detected in the urine. On the same day the pancreatic juice, obtained by duodenal tubing and incubated at 38 C. for thirty minutes, yielded 160 Willstätter units—a low normal—of amylase and only traces of trypsin; when incubated for twenty-four hours it yielded 32 units of trypsin, that is, about a tenth of the normal, and 8 units of lipase, or practically none.

Except for the first day of pancreatic involvement, the temperature never exceeded 37.5 C. (99.5 F.), the child had no complaints, except sometimes a slight pain on palpation of the left upper abdominal quadrant, and continued to play. The condition remained unchanged even when the signs of pancreatitis reached their maximum on the fifteenth and the sixteenth day. Data then obtained were as follows: Blood sugar was 170 mg. per hundred cubic centimeters. There were small amounts of sugar in the urine. Of the 30 Gm. of fat eaten, 19.60 Gm., or about 65 per cent, reappeared in the feces, and 60 per cent of this was in unsplit condition. The lipolytic activity of the pancreatic juice was 7 units after incubation at 38 C. for twenty-four hours, or practically none, and the tryptic activity was 20 units, or very low. The amylolytic activity after incubation at 38 C. for thirty minutes was 64 Willstätter units, or low. At the same time the sodium arsanilate–stable lipase in the blood rose to 136 units and the amylase to 128 Willstätter units after incubation at 38 C. for thirty minutes, while the amylase in the urine was 512 Willstätter units.

The child was treated with mild mercurous chloride and quinine for three days with no result whatever and subsequently with acetarsone, 0.12 Gm. once

daily for two days and 0.25 Gm. once daily for three consecutive days. What effect this had is doubtful, but the diabetic symptoms ceased in a week and digestion of protein also became normal. A fortnight later, however, although he was on an almost fat-free diet, digestion of fats still proved to be deficient. Then, on the thirty-second day, about 50 per cent of the fat eaten was eliminated, 46 per cent of it being unsplit; lipase was present only in traces, and urinary diastase after incubation at 38 C. for thirty minutes was 48 Willstätter units. The condition finally returned to normal in the sixth week, when both enzyme values and fat metabolism were completely restored. At present, five years later, the child is in excellent health and his digestion is faultless.

It can be seen from this case that an inflammation of the pancreas need by no means present stormy symptoms and, what is more, that it may take rather a disguised course, as in the case reported, in which the bulky and offensive stools had presented the only manifest sign. It is possible that, as is taught, the inflammation itself may subside in four to six days. On the other hand, however, the deficiency symptoms caused may remain unchanged for weeks. It is characteristic, as was found by Racugno and Manca [20] and by others, and proved in various other conditions, that the formation of lipase is the process most easily affected. A deficiency in this enzyme was the first sign of the condition and the last to disappear in the case reported, while its presence in the blood confirmed Simon's [21] statements.

The symptoms of secondary pancreatitis mostly disappear within a few weeks. This is, however, not a rule without exceptions, as will be seen in the next case selected.

CASE 2.—N. M. was a girl of 7 years. The family history was not significant. She had had no illness until the age of 5½ years. Then she had been thoroughly examined as a member of a control group of healthy children for some metabolism studies, and all her enzymes and digestion values were found to be normal. A month later she contracted scarlet fever. She had no fever apart from the first few days, and seemingly no complications whatever occurred. From that time she had not been ill but constantly lost weight, having foul stools several times a day.

Physical examination revealed a pale, weak child of normal height but somewhat retarded in development, her weight being 19.40 Kg., a retardation of nine months. One and a half years before, her weight had been that of a child fourteen months older. The muscles were a little flabby. Examination revealed nothing abnormal, and neither the liver nor the spleen was palpable. Blood tests for syphilis, intradermal tests for tuberculosis and urinalysis gave negative results. Analysis of the blood revealed a slight anemia; blood sugar was 92 mg. per hundred cubic centimeters. She had one or two large pasty, foul stools a day. Parasitologic examinations were negative in result. From the time that she had scarlet fever the child would not eat butter and vomited if given rich foods. Gastric examination showed an evacuation time above three hours, 16 cc. of free hydrochloric acid, 25 cc. of bound hydrochloric acid and 50 cc. of total acids. There were only traces of lipase and normal amounts of pepsin. With duodenal

20. Racugno and Manca: Arch. ital. di pediat. **8**:132, 1940.
21. Simon, H.: Ergebn. d. inn. Med. u. Kinderh. **32**:83, 1927.

tubage 3 cc. of pancreatic juice was gained. After incubation at 38 C. for twenty-four hours the lipase activity in terms of cubic centimeters of tenth-normal sodium hydroxide was 0.32 and the trypsin was 128 units, both values being extremely low. After incubation at 38 C. for thirty minutes the amylase was 320 Willstätter units, however, or around normal. There was no further secretion after administration of milk, but 12 cc. more after administration of secretin. This yielded the same value for lipase activity (0.32), a somewhat higher value for trypsin (256 units) and the approximately normal amount of 640 Willstätter units of amylase after thirty minutes of incubation at 38 C. There was no sodium arsanilate-stable lipase to be found in the blood. The diastase level was found normal in both blood and urine. Of 100 Gm. of oil ingested, 60 Gm. was voided with the feces, 47 Gm. of it unsplit. Only extremely small amounts of lipase could be detected in the feces, while nuclease activity, according to a test performed with goose blood, seemed normal. The findings were further confirmed by the fact that after administration of lipase for three days, when a test meal containing 100 Gm. of olive oil was given together with 400 Rona units of lipase, no more than 11 Gm. of fat was excreted, 87 per cent of it in split condition. Three days after discontinuation of the administration of lipase, the original state was found to prevail. When the child was examined three months later this condition was found unaltered. Different extracts of pancreas were given, but no improvement could be attained.

The disturbance of fat digestion in this child arose, in all probability, from the sequelae of a previous inflammation of the pancreas, and it may be assumed that the pancreatitis was a complication of scarlet fever. The splitting of a part of the fat in the feces, a phenomenon which sometimes occurs even in complete dysfunctions of the pancreas, must be ascribed to bacterial action, as has been pointed out by Gross [19c] and Arndt and Welcker.[22] The split part of the fat is, however, of no use to the organism, lipolysis occurring far beyond those parts of the intestine that are capable of absorbing fat.

Pancreatic dysfunction of a much slighter degree may lead to hypertrophy, even in those cases in which usual laboratory methods, while revealing a somewhat lessened production of enzymes and especially of lipase, show no deficiency whatever or at most negligible alterations in fat metabolism. This has been found by Kitaigorodskaja [23] and Frenkel [24] and by my own unpublished observations. An insufficiency of the pancreas must, sooner or later, give rise to symptoms of the celiac syndrome. The lack of fat and of the various substances that are absorbed together with it stop development and cause anemia and hypovitaminoses. This will be shown by the next case.

Case 3.—J. L. was a boy of 4½ years of a healthy family with 4 normal siblings. He had had no illness until one and one-half years previously, when he contracted parotitis, which subsided seemingly without complications within a week. Two

22. Arndt, H. J., and Welcker, A.: Ztschr. f. Kinderh. **41**:518, 1926.
23. Kitaigorodskaja, O.: Ztschr. f. Kinderh. **50**:748, 1931.
24. Frenkel, I. L.: Pediatria, 1940, no. 2-3, p. 22.

months later, however, it was noted that the weight of the child (17 Kg.), which had hitherto developed normally, tended to decrease and that his stools also changed in character, becoming more frequent and offensive. He continued to lose weight and just prior to admission had two attacks of tetany.

Diagnosis on admission was celiac disease. The child, weighing then only 9.60 Kg., was extremely emaciated, and the wasting of the buttocks together with a distended abdomen, the atonic muscles, the dry, flaccid skin, his small head with scanty hair, the tetany and the characteristic fatty stools all pointed to that disease. Examinations, however, revealed a complete pancreatic insufficiency.

On examination signs of rickets were seen. Heart and lungs were normal. Neither the liver nor the spleen was palpable, and the temperature was normal. Reactions to blood tests for syphilis and intradermal tests for tuberculosis were negative, and the urine was normal. The hemoglobin content was 74 per cent, and the erythrocytes numbered 2,850,000 and the leukocytes 6,800, with normal differential count. The calcium content of the serum was 10.0 mg. per hundred cubic centimeters, the phosphorus 6.90 mg., the total proteins 6.40 Gm. and the sugar 81 mg. The dextrose test curve was somewhat elevated, with a peak at 196 mg. after sixty minutes. Passage roentgenograms of the bowels showed a gastric evacuation time beyond three hours, normal small intestines with motility not increased but a dilated colon revealing almost no contours. After a mixed diet the feces contained 15 per cent dry substance, of which 24 per cent was fat, and of this 79 per cent was unsplit, 10 per cent was fatty acids and 11 per cent was soaps. The p_H was 6.9. After a diet containing 60 Gm. of olive oil, 49.10 Gm., i. e., 81 per cent, of the ingested amount was excreted, 68 per cent of it in an unsplit state. The duodenal juice contained amylase in more or less normal amounts but only 10 to 15 per cent of trypsin and not even traces of lipase. In the blood there was no sodium arsanilate–stable lipase, while amylase activity was normal in both blood and urine. The gastric juice contained no lipase but normal amounts of pepsin.

Thus the analyses disclosed, besides a somewhat lessened production of proteolytic enzymes, a total lack of fat-splitting ones. Both for control measures and for therapeutic purposes the pancreatic juice of a healthy man was given for three consecutive days, the pancreatic extracts at my disposal at that time containing, according to several tests, no active lipase. A fecal analysis was made on the third day, and it was found that while the child was on the same diet as before, only 4.10 Gm. of fat, that is, about one sixth of that originally found, was excreted and no more than 20 per cent of it was unsplit, demonstrating that if the fat is being well digested the absorption capacity is unimpaired. The tolerance test was then repeated with simultaneous administration of lipase. After the intake of 60 Gm. of olive oil, only 11 Gm. was excreted, i. e., 14 per cent of the ingested amount, and this contained only 2.30 Gm., that is, hardly more than 20 per cent, unsplit parts. When the administration of the pancreatic juice was discontinued, the original imperfect state was reestablished at once, the greater part of the fat ingested not being absorbed. Subsequently, big doses of pancreatic extracts were prescribed to be taken permanently, and the child was dismissed.

He died twenty months later in a Transylvanian hospital. Owing to wartime difficulties no detailed information could be received as to his terminal state except that on admission he had been "extremely emaciated," that he died of "inanition and atrophy" and that no pathologic changes were revealed by the necropsy except a "small, hard and fibrous pancreas."

COMMENT

The conclusion to be drawn from the cases reported is that pancreatitis is far from being a rare involvement of certain diseases. In the acute stage, however, it takes a much milder course than in the grave illnesses generally known. It may be disclosed in its acute stage by nothing more than the lessened production of some enzymes, and it is only much later that digestive deficiencies, frequently appearing with consequent impairment of the development, point to it. There is—perhaps just because of the lack of experience—no routine treatment known in the acute stage, but one may suppose that in suitable cases sulfonamide drugs, blood transfusions and penicillin, together with the hitherto successfully used reconvalescent serums and arsenic, will be of help. It is important that the condition be diagnosed in its earliest stage, as the process is no longer reversible after it has become chronic and if once deficiencies have arisen it is almost impossible to keep the state of the patient even stationary. Such cases require, apart from large doses of pancreatic extracts or enzyme preparations, an almost fat-free diet. (It is interesting to note how this restriction is spontaneously observed by some patients. Both the children reported on in cases 2 and 3 had to be forced to swallow rich fatty foods, while they were always willing to consume large amounts of dry cakes or vegetables.) If gastric lipase is present, milk can render good services but butter or cream are not indicated. One is bound to doubt whether those cases of celiac disease which were reported to have shown dramatic responses to the treatment with human milk, formerly often advocated, really were genuine ones or only lipase deficiencies, the temporary improvement of which was due to the fat-splitting capacity of that enzyme contained in the milk itself or in the gastric juice. The parenteral administration of vitamins A, D and K is, of course, of extreme importance. With the aid of all these, the condition of the patients can be if not ameliorated at least kept stable, but unfortunately never permanently.

SUMMARY

Pancreatitis, rather contrary to the general supposition, is a frequent complication of certain diseases, but it may subside without stormy symptoms and only the lessening of some enzymes, especially lipase, and the resulting deficiency conditions leading to celiac syndrome may point back to it. Three selected cases are presented, a case of mild pancreatitis following parotitis, one of severe pancreatitis following scarlet fever and a third case due to parotitis that ended fatally.

FACTORS INFLUENCING RETENTION OF NITROGEN AND CALCIUM IN PERIOD OF GROWTH

VII. Effect of Methyl Testosterone

JOSEPH A. JOHNSTON, M.D.
DETROIT

SKELETAL growth terminates with the attainment of sexual maturity and is a function of physiologic age rather than of chronologic age. In this series of studies, nitrogen was chosen as an indispensable component of active protoplasmic tissue and calcium as an essential element of the skeletal system, and their balances were determined under a variety of circumstances. In the period of growth that precedes sexual maturity, the factors—dietary, infectious and hormonal—that affect one of these tends in a general way to exert a similar effect on the other. After puberty, it might be anticipated that the fate of these two items would differ; the need for the storage of calcium is passing, the sharp acceleration of growth in height changing to a decelerating phase synchronously with the attainment of sexual maturity, but considerable growth involving the storage of nitrogen will be involved in the development of the sexual apparatus, as well as an increase in muscle mass. In the case of the estrogens, I have shown [1] that the creation of an excess of these by the administration to normal girls of estrone resulted in a diminution in the storage of calcium and in most instances of nitrogen also. Testosterone, however, has been shown repeatedly [2] to exert a markedly anabolic effect on nitrogen, but, so far as I have been able to find, there are no available studies of its effect on the calcium balance. Talbot and his co-workers [3] determined

1. Johnston, J. A.: Factors Influencing Retention of Nitrogen and Calcium in Period of Growth: IV. Effect of Estrogen, Am. J. Dis. Child. **62**:708 (Oct.) 1941.

2. (*a*) Kochakian, C. D., and Murlin, J. R.: The Effect of Male Hormone on the Protein and Energy Metabolism of Castrate Dogs, J. Nutrition **10**:437 (Oct.) 1935; (*b*) The Relationship of the Synthetic Male Hormone, Androstendion, to the Protein and Energy Metabolism of Castrate Dogs, and the Protein Metabolism of a Normal Dog, Am. J. Physiol. **117**:642 (Dec.) 1936. (*c*) Kochakian, C. D.: Testosterone and Testosterone Acetate and the Protein and Energy Metabolism of Castrate Dogs, Endocrinology **21**:750 (Nov.) 1937. (*d*) Kenyon, A. T.; Knowlton, K.; Sandiford, I.; Koch, F. C., and Lotwin, G.: A Comparative Study of the Metabolic Effects of Testosterone Propionate in Normal Men and Women and in Eunuchoidism, ibid. **26**:26 (Jan.) 1940.

3. Talbot, N. B.; Butler, A. M.; Pratt, E. L.; MacLachlan, E. A., and Tannheimer, J.: Progeria: Clinical, Metabolic and Pathologic Studies on a Patient, Am. J. Dis. Child. **69**:267 (May) 1945.

the fecal and urinary output in a single case of progeria in which treatment was with testosterone, but it was not possible to calculate the balance from their data, as the stool losses of the control period were averaged with those of the period during which testosterone was administered, and, as will be shown here, the most striking effect of testosterone is on the fecal loss. A definite rise in the basal metabolism has been observed with methyl testosterone but no significant change with testosterone propionate[4] except in the eunuchoid.[4b] That calcium metabolism might be affected by testosterone is suggested not only by the reciprocal relationship between skeletal growth and sexual maturity, but also by (1) the observation that large doses caused epiphyseal union to take place at a more rapid rate than normal,[5] and (2) the fact that the depression of growth in body weight and length in castrate male rats with large doses proved greater than occurred with castration alone.[6] Wentworth and his colleagues,[7] while demonstrating that estradiol-benzoate given to mice resulted in a significantly higher concentration of inorganic substance in the femora and pelves, got no such change with testosterone. Armstrong and his co-workers[8] demonstrated a reduction of ash in the humeri of rats with both orchidectomy and the daily administration of large doses of testosterone propionate. Atrophy of the bone which followed orchidectomy was prevented by the administration of large doses of testosterone. They speak of it as "paradoxical" that both castration and plethora of an androgenic hormone produced a decrease in ash content, and yet by analogy this is to be expected; in our thyroid studies,[4b] the retention of calcium was affected adversely as much by a deficiency of the hormone as by an excess, and the effect of administering any hormone will apparently be conditioned by whether or not it achieved replacement to an optimal level or created a plethora.

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4. (*a*) Kenyon and others.[2d] (*b*) Johnston, J. A., and Maroney, J. W.: Factors Affecting Retention of Nitrogen and Calcium in Period of Growth: I. Effect of Thyroid on Nitrogen Retention, Am. J. Dis. Child. **58**:965 (Nov.) 1939. (*c*) McCullagh, E. P., and Rossmiller, H. R.: Methyl Testosterone: II. Calorigenic Activity, J. Clin. Endocrinol. **1**:503 (June) 1941.

5. McCullagh, E. P., and McGurl, F. J.: The Effects of Testosterone Propionate on Epiphyseal Closure, Sodium and Chloride Balance and on Sperm Counts, Endocrinology **26**:377 (March) 1940.

6. Rubinstein, H. S., and Solomon, M. L.: The Growth Depressing Effect of Large Doses of Testosterone Propionate in the Castrate Albino Rat, Endocrinology **28**:112 (Jan.) 1941.

7. Wentworth, J. H.; Smith, P. K., and Gardner, W. U.: The Composition of Bones of Mice Receiving Estrogens and Androgens, Endocrinology **26**:61 (Jan.) 1940.

8. Armstrong, W. D.; Knowlton, M., and Gouze, M.: Influence of Estradiol and Testosterone Propionataes on Skeletal Atrophy from Disuse and on Normal Bones of Mature Rats, Endocrinology **36**:313 (May) 1945.

Stimulation in linear growth with testosterone has been reported.[9] McCullagh and McGurl noted that, while small doses (15 to 60 mg. per week) caused no distinct advance in epiphyseal age, larger amounts (105 mg. or more weekly) caused a two year increase in bone age in eight months.

There are presented here the balances for nitrogen and calcium and determinations of the basal metabolism of 5 boys, aged 7 years to 15 years, before, during and after the daily administration of 10 mg. of methyl testosterone by mouth. The methods are described in the first two papers of the series.[10] In brief, six rotating diets are used, a pooled sample consisting of one sixth of each day's diet being analyzed for calcium and nitrogen. A minimum of eighteen days is felt essential for significance in the case of calcium. The figure recorded for basal calories represents the average of all determinations within an eighteen day period, an estimation being made every six days. The subjects received 10 mg. of methyltestosterone by mouth daily.

SUBJECTS

R. C. was a 7 year old boy admitted in February 1945 for the treatment of tuberculous cervical adenitis. The chest was clear. The glands were resected uneventfully in June, and the observations here recorded were made six months after his operation, January to April 1946, during which time he was active and attending school in the convalescent home.

E. D. was a 10 year old boy who was considered to have a healed tuberculous hip for three years and was hospitalized at this time for orthopedic procedures to influence contractures and to induce an epiphyseal arrest. Balance study extended from June 5 to July 29. During part of that time (until July 20) he was in a plaster cast. He gained 8 pounds (3.6 Kg.). The calcium, phosphorus and phosphatase levels in the blood were normal. The chest was normal.

T. A. was a 10 year old boy admitted for observation for tuberculosis at the request of the Board of Health. No evidence of this was found, tuberculin tests and roentgenograms of the chest revealing no abnormality. He remained in, however, because of a situation at home. He was active and attending school during the observation. He gained 10 pounds (4.5 Kg.) in weight.

G. W. was a 15 year old boy hospitalized for grafting of skin over old wounds resulting from a burn two years previously. The balance study ran from April 28 to June 2 and was interrupted one day by a grafting procedure on May 1.

O. H. was a 14 year old boy hospitalized for the treatment of a slipped femoral epiphysis. The operative procedure was carried out on September 10;

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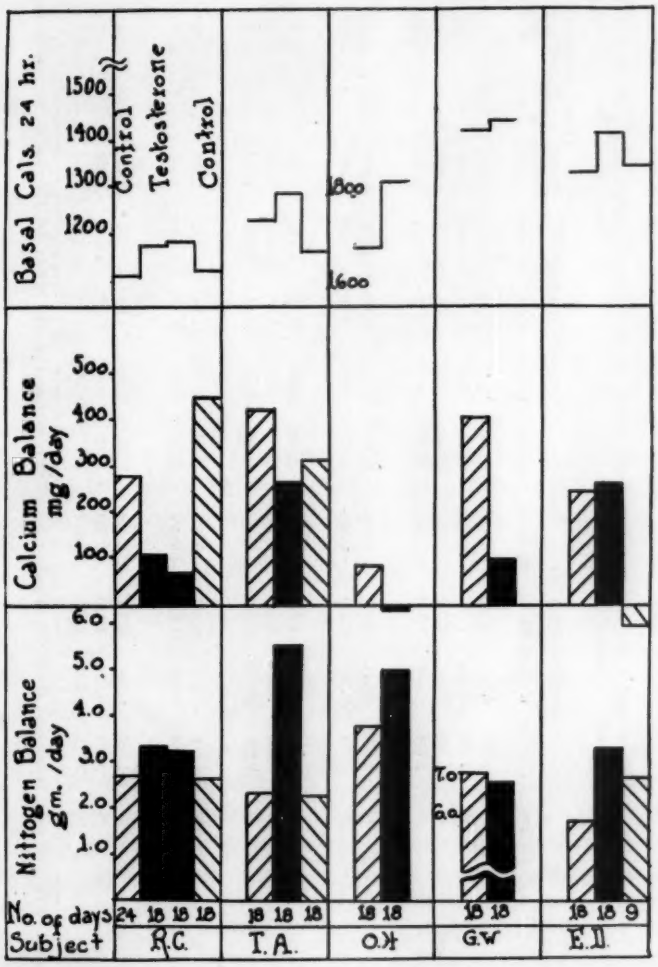
9. Dorff, G. B.: Rapid Growth in Height Produced by Chorionic Gonadotropin in a Dwarfed Infantile Identical Twin, J. Clin. Endocrinol. **1**:940 (Dec.) 1941. McCullagh, E. P., and McGurl, F. J.: The Effects of Testosterone Propionate on Epiphyseal Closure, Sodium and Chloride Balance and on Sperm Counts, Endocrinology **26**:377 (March) 1940.

10. Johnston, J. A., and Maroney, J. W.: Factors Affecting Retention of Nitrogen and Calcium in Period of Growth: II. Effect of Thyroid on Calcium Retention, Am. J. Dis. Child. **58**:1186 (Dec.) 1939; footnote 4 *b*.

sutures were removed on September 18, and the balance study was conducted from September 21 through October 26. During the first week he was in a cast. From September 29 on he received daily treatments in the Hubbard tank.

OBSERVATIONS

The increased storage of nitrogen and the elevation of the basal metabolic rate noted by others are confirmed here. The only exception



Effect of methyl testosterone on metabolism. The cross hatched columns represent control periods, and the solid black, periods in which testosterone was being administered. Determinations of the metabolic rate were made every six days, and the figure recorded for an eighteen day period is an average of these. There are demonstrated a slight increase in basal calories, a definite reduction in retention of calcium and an increase in retention of nitrogen with comparatively large amounts (10 mg. daily for eighteen days) of methyl testosterone administered to presumably normal boys in the growth period.

Balances for Nitrogen and Calcium and Determinations of the Basal Metabolism of Five Patients

Subject	Days	Calcium, Gm./Day				Nitrogen, Gm./Day				Basal Calories, 24 Hr.	Basal Metabolic Rates *		Respiratory Quotient	Weight, Pounds	Height, Inches	Diet, Calories
		Intake	Urine	Stool	Balance	Intake	Urine	Stool	Balance		B.	W.				
R. C.																
Control	24	1.739	0.082	1.360	+0.297	12.30	8.13	1.46	+2.71	1,104	− 6	+ 3	0.80	60	49	1,900
Testosterone	18	1.714	0.040	1.565	+0.109	12.37	7.56	1.47	+3.34	1,173	± 0	+ 3	0.81	60½		
Testosterone	18	1.729	0.016	1.642	+0.071	12.33	7.43	1.60	+3.30	1,179	+ 2	+ 5	0.78	60¼		
Control	18	1.724	0.014	1.258	+0.452	12.26	8.26	1.36	+2.64	1,123	− 4	± 0	0.78	60¾		
O. H.																
Control	18	1.399	0.241	1.072	+0.086	14.83	9.96	1.16	+3.71	1,688	−15	+ 2	0.75	146	68	2,400
Testosterone	18	1.284	0.133	1.159	−0.008	15.07	8.84	1.25	+4.98	1,829	− 8	+10	0.76	149½		
E. D.																
Control	18	1.328	0.132	0.945	+0.246	13.79	10.92	1.13	+1.74	1,336	− 3	+ 3	0.78	79	59	2,200
Testosterone	18	1.337	0.137	0.942	+0.258	13.80	9.21	1.30	+3.29	1,414	+ 3	+ 9	0.80	79		
Control	9	1.279	0.137	1.182	−0.040	14.76	10.72	1.35	+2.69	1,344	± 0	+ 5	0.75	73½	(east off)	
G. W.																
Control	18	1.396	0.135	0.853	+0.408	16.06	7.99	1.09	+6.98	1,428	− 8	+ 1	0.84	97¼	61¼	2,000
Testosterone	18	1.434	0.085	1.250	+0.099	16.73	8.40	1.49	+6.84	1,441	− 7	+ 2	0.82	97½		
T. O.																
Control	18	1.353	0.226	0.694	+0.433	15.44	12.01	1.06	+2.37	1,233	−13	− 5	0.88	78½	57½	2,000
Testosterone	18	1.508	0.099	1.140	+0.269	17.85	10.92	1.39	+5.54	1,296	− 8	− 1	0.86	82¼		
Control	18	1.577	0.077	1.205	+0.295	17.07	13.25	1.52	+2.30	1,164	− 9	− 1	0.87	84		

* B. refers to the basal metabolic rate calculated from the Boothby-Sandiford tables and W. refers to the basal metabolic rate calculated from the Wetzel tables.

(G. W.) may represent the interesting phenomenon of the physiologic ceiling, an already inordinately high retention falling very slightly.

In the case of calcium, there is a consistent fall in the urinary output, but a larger rise in the fecal excretion, resulting in a diminished retention. In one instance (E. D.) no change was noted in the eighteen days during which the material was given but in the next nine days a large loss occurred; this would not ordinarily be counted as a significantly long period, but it represented an uninterrupted continuance of the observation and the amount was significantly large. The low retention recorded in the control period of the boy with the slipped femoral epiphysis (O. H.) was previously noted in 2 other cases;[8] the balance became negative after the use of methyl testosterone.

COMMENT

In interpreting an observation such as this, it should again be pointed out that, among the many items conditioning the action of a hormone, one outstanding one will be whether or not the material administered supplies a defect or creates an excess; presumably it is the latter which was being measured. It is probable too that a different effect would result from the administration of androgens to the female; the subjects were all male. Finally, as in the case of divergent reports on the effect of estrogens on retention of calcium the age of the subject would be expected to play a role, and it would not be surprising if quite different effects followed the use of this material in the aged.

SUMMARY

Methyl testosterone given by mouth to 5 growing boys caused a diminished urinary output of calcium and an increased fecal loss, with a significantly diminished balance. Storage of nitrogen was increased and the basal metabolism slightly elevated.

NOTE.—Since this paper was submitted for publication, there has appeared a study (Reifenstein, E. C., Jr., and Albright, Fuller: The Metabolic Effects of Steroid Hormones in Osteoporosis, *J. Clin. Investigation* **26**:24 [Jan.] 1947) in which the effect of testosterone on the calcium balances of adults with senile osteoporosis and Cushing's syndrome was anabolic and reduction occurred in both urinary and fecal output. It appeared to me that the most likely explanation for the discrepancy between my observations and those reported in these adults would be that offered in my comment, namely, that creation of an excess might be expected to be catabolic when the correction of a deficit was anabolic.

Dr. O. H. Gaebler supervised the balance determinations and Dr. F. W. Hartman the determinations of the basal metabolism.

Case Reports

ISLET CELL TUMOR OF PANCREAS IN A NEWBORN INFANT (NESIDIOBLASTOMA)

HARRY SHERMAN, M.D., BROOKLYN

SPONTANEOUS hypoglycemia due to insular tumor of the pancreas (nesidioblastoma [1]) in the neonatal period is a rare disease. My patient was subjected to rather extensive clinical study and, to my knowledge, is the youngest one on record to have been surgically explored in quest of such a tumor. Final corroboration was obtained at autopsy.

The concept of hyperinsulinism is intimately linked with the development of knowledge concerning the internal secretory function of the pancreas and its relation to diabetes. True hyperinsulinism is the antithesis of diabetes (Wilder).[2] The discovery of the islet tissue by Langerhans in 1869 [3] and the demonstration that these nests of cells are distinct from the acinar tissue laid the foundation of present knowledge. The experiments in ligation of the ducts by Arnozan and Vaillard,[4] showing atrophy of the acinar tissue and persistence of the islets, further proved the distinctive character of the islet tissue. In 1890 Minkowski and von Mering,[5] and two years later Minkowski,[6] proved beyond any doubt that diabetes can be produced experimentally by total pancreatectomy and even postulated that the pancreas has an endocrine

From the Department of Pediatrics, Jewish Hospital of Brooklyn; Dr. Benjamin Kramer, Pediatrician in Chief.

1. Laidlaw, G. G.: Nesidioblastoma: Islet Tumor of Pancreas, Am. J. Path. **14**:125, 1938. Laidlaw, feeling the need for a terse, definitive name for adenoma of the islets of Langerhans, introduced the term "nesidioblastoma." The cells derived from the duct epithelium and destined to form islets are called nesidioblasts. A tumor formed from these "islet builders" is called a nesidioblastoma.

2. Wilder, R. M.: Clinical Diabetes Mellitus and Hyperinsulinism, Philadelphia, W. B. Saunders Company, 1940.

3. Langerhans, P.: Beiträge zur mikroskopischen Anatomie der Bauchspeicheldrüse, Berlin, Lange, 1869.

4. Arnozan, X., and Vaillard, L.: Contribution a l'étude du pancreas du lapin; lésions provogées par la ligature du canal de Wirsung, Arch. de physiol. norm. et path. **3**:287, 1884.

5. Minkowski, O., and von Mering, J.: Diabetes mellitus nach Pankreasextirpation, Arch. f. exper. Path. u. Pharmakol. **26**:371, 1890.

6. Minkowski, O.: Weitere Mittheilungen über den Diabetes mellitus nach Extirpation des Pankreas, Klin. Wchnschr. **29**:90, 1892.

function. It remained for Laguesse [7] to describe fairly accurately the microscopic anatomy of the islet cells. Ssobolew in 1900 [8] was the first investigator to forecast the eventual organotherapy of diabetes.

In the eventful year 1922, marking a new era in medicine, Banting and Best [9] announced the practical production of the active principle of the islands of Langerhans (later called insulin) and clearly showed that this particular pancreatic extract can be successfully used in the treatment of diabetes. The concept of hyperinsulinism logically followed in the wake of this great stride. Observations were made by Banting and his associates and by many others who were using insulin therapeutically that overdoses of insulin could produce hypoglycemia with a characteristic complex of symptoms. In 1924 Seale Harris [10] propounded the existence, clinically, of spontaneous hypoglycemia due to overactive islet tissue, a result of hyperplasia or neoplasm.

In 1920 came the first report, by Dubreuil and Anderodias,[11] of the observation at autopsy of hypertrophied islets in a newborn infant of a diabetic mother. Gray and Feemster [12] were the first in this country to demonstrate the hyperplastic insular tissue with associated hypoglycemia in an infant of a diabetic mother. The association of neoplasm of the islets with spontaneous hypoglycemia was first shown by Wilder and his associates,[13] in a case in which there had been surgical removal of an islet cell tumor followed by the observation at necropsy of similar metastatic carcinomatous tumors in the liver, from which were extracted large amounts of insulin.

The clearer understanding of hyperinsulinism has brought forth a large number of clinical studies and detailed descriptions of the pathologic changes of insular tumors, notable among which are those by Whipple

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7. Laguesse, E.: Sur la formation des ilôts de Langerhans dans les pancréas. Compt. rend. Soc. de biol. **45**:819, 1893.

8. Ssobolew, L. W.: Ueber die Structur der Bauchspeicheldrüse unter gewissen pathologischen Bedingungen, Zentralbl. f. allg. Path. u. path. Anat. **11**:202, 1900.

9. Banting, F. G., and Best, C. H.: Internal Secretion of the Pancreas, J. Lab. & Clin. Med. **7**:251, 1922. Banting, F. G.; Best, C. H., and others: Pancreatic Extracts in the Treatment of Diabetes Mellitus, Canad. M. A. J. **12**:141, 1922.

10. Harris, S.: Hyperinsulinism and Dysinsulinism, J. A. M. A. **83**:729 (Sept. 6) 1924.

11. Dubreuil, G., and Anderodias: Ilôts de Langerhans chez un nouveau né, issu de mère glycosurique, Compt. rend. Soc. de biol. **83**:1490, 1920.

12. Gray, S. H., and Feemster, L. C.: Compensatory Hypertrophy and Hyperplasia of the Islands of Langerhans in the Pancreas of a Child Born of a Diabetic Mother, Arch. Path. **1**:348 (March) 1926.

13. Wilder, R. M.; Allan, F. N.; Power, M. H., and Robertson, H. E.: Carcinoma of the Islands of the Pancreas with Hyperinsulinism and Hypoglycemia, J. A. M. A. **89**:348 (July 30) 1927.

and Frantz,[14] Frantz,[15] O'Leary and Womack,[16] Laidlaw,[1] Brunschwig,[17] Gomori [18] and Duff and Murray.[19]

For the proper evaluation of symptoms and for differential diagnosis the following classification of hypoglycemia is given, a modification of that presented by Hartmann and Jaudon [20]:

Classification of Hypoglycemia

A. True hyperinsulinism (excess of insulin)
   1. Hyperactivity of islands of Langerhans
      (*a*) Physiologic hyperactivity (induced by excessive carbohydrate intake)
      (*b*) Hypertrophy or hyperplasia (compensatory or pathologic)
      (*c*) Tumors of the islets of Langerhans
   2. Administration of insulin

B. Relative hyperinsulinism
   1. Lack of substances which are precursors of dextrose
      (*a*) Diminished absorption from gastrointestinal tract
         (1) Starvation
         (2) Loss because of vomiting, diarrhea or fistula, with or without infection (combination of diminished intake of food and increased metabolism)
      (b) Abnormalities of the liver as in von Gierke's disease, primary or metastatic carcinoma, acute yellow atrophy, cirrhosis, diphtheria, poisoning with arsphenamine and other substances, fatty infiltration of the liver and chronic infectious hepatitis.
      (*c*) Wasting of the muscles with depleted stores of glycogen.
   2. Lack of development or breakdown of regulatory mechanism
      (*a*) Normal newborn or premature infant
      (*b*) Endocrine imbalance
         (1) Insufficiency of adrenal cortex as in adrenal hemorrhage, Addison's disease or tumor (tuberculosis of adrenal gland with cortical hypofunction), Waterhouse-Friedrichsen syndrome (epidemic cerebrospinal meningitis [meningococcic]), insufficiency of compound "E" of Kendall (11-dehydro-17-hydroxycorticosterone)

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14. Whipple, A. O., and Frantz, V. K.: Adenoma of Islet Cells with Hyperinsulinism: A Review, Ann. Surg. **101**:1299, 1935.

15. Frantz, V. K.: Tumors of Islet Cells with Hyperinsulinism, Benign, Malignant and Questionable, Ann. Surg. **112**:161, 1940.

16. O'Leary, J. L., and Womack, N. A.: Histology of Adenoma of the Islets of Langerhans, Arch. Path. **17**:291 (March) 1934.

17. Brunschwig, A.: Large Islet Cell Tumor of the Pancreas, Surgery **9**:554, 1941.

18. Gomori, G.: Pathology of the Pancreatic Islets, Arch. Path. **36**:217 (Aug.) 1943.

19. Duff, G. L., and Murray, E. G. D.: Pathology of Islet Cell Tumors of the Pancreas, Am. J. M. Sc. **203**:437, 1942.

20. Hartmann, A. F., and Jaudon, J. C.: Hypoglycemia in Childhood, J. Pediat. **11**:1, 1937.

(2) Hypophysial disorders as in Simmond's disease (hypopituitary cachexia), tumor, dwarfism
(3) Hypothyroidism
(*c*) Disturbances of the nervous system
(1) Functional disturbances of the sympathetic system
(2) Organic disease of the nervous system—intracranial injury, tumor
(*d*) Moribund state

C. Miscellaneous
Renal glycosuria, eclampsia, fatigue, progressive muscular dystrophy, exercise, lactation, status thymicolymphaticus

D. Cryptogenic

REPORT OF A CASE

Baby F. H. was a white girl born on Feb. 8, 1945.

Family History.—The mother is 21 years of age, living and well. The father is 22 years of age, living and well. There is a high incidence of familial endocrine disturbances on the maternal side: (*a*) The maternal grandfather had an undescended testicle; (*b*) 2 maternal grandaunts were operated on for exophthalmic goiter; (*c*) 1 maternal grandaunt was operated on for "ovarian trouble"; (*d*) another maternal grandaunt had amenorrhea at 30 years of age; (*e*) 2 maternal second cousins have been treated for pituitary disturbances and (*f*) another maternal second cousin, aged 10 years, has been treated for diabetes for the past four years.

Antepartum History.—The period of gestation was 40 weeks. The mother's Kline reaction was negative. The mother's urine was normal throughout the pregnancy. No reducing substances were found in the urine. During the last four months of the pregnancy the mother consistently complained of pronounced fetal movements. The blood pressure remained within normal limits. During the last three months of gestation the mother also complained of increasing fatigue and listlessness. She had repeated spells of headache, drowsiness and fatigue so great as to cause her to seek bed rest and to sleep for hours at a time, at the same time sweating profusely. There was no gain in weight during the first four months. The total gain in weight at term was 17 pounds (7.7 Kg.). The mother's weight after delivery was 4 pounds (1.8 Kg.) less than before the pregnancy began. The results of the maternal postpartum dextrose tolerance test were within normal limits. The first stage of labor lasted eleven and one-half hours. The second stage lasted three hours. The head was in a right occipito-anterior position. Low forceps were applied. The weight at birth was 8 pounds, 13 ounces (3,997 Gm.). The infant's condition at birth was reported as good and her cry lusty. No respiratory stimulation was necessary. There was slight molding of the head with a slight caput on the occiput.

Course.—The child apparently behaved normally until twenty-four hours after delivery, when twitchings were noted involving all extremities, the neck and the face. Respirations were described by the nurse in charge as irregular with frequent periods of apnea and intermittent cyanosis. During the height of the generalized twitchings the child became cyanotic and covered with a profuse cold and clammy perspiration and emitted a sharp cerebral type of cry. Before any therapy was begun a sample of the blood was taken for determination of calcium, urea nitrogen and sugar.

The infant was given vitamin K (menadoine bisulfite, 2 mg.) intramuscularly, oxygen by funnel, calcium lactate by mouth, calcium gluconate intravenously and small amounts of glucose water by mouth, which it took fairly well. Hypodermic administration of phenobarbital sodium was ordered to control the twitchings. Toward the evening of the second day of life the temperature rose to 102.2 F. At this time the child appeared drowsy. The color remained good while the child was receiving oxygen by funnel, but with its withdrawal cyanosis supervened. All extremities were spastic. Occasional twitchings were noted involving the face and the upper extremities. There was a mild but definite jaundice. Breathing was shallow and occasionally catchy with periods of apnea. The head showed a slight occipital caput. The anterior fontanel was under normal tension. There was no separation of the suture lines. The ears, the nose and the throat appeared normal. The heart was not enlarged to percussion, and the sounds were of good quality. There was a rather loud systolic murmur heard over the entire left side of the precordium, loudest over the lower part of the sternum and not transmitted either to the neck or to the axilla. The lungs were clear to percussion and auscultation. The abdomen was soft. The kidneys, the liver and the spleen were not palpable. The cord was attached and normal. The genitalia were normal. The toes were kept in a constant Babinski position with dorsiflexion of the big toes and plantar flexion with spreading of the other toes. There was diminished turgor of the skin with a definite lag. The infant was given a clysis of 5 per cent dextrose in isotonic solution of sodium chloride, after which the twitchings diminished and the temperature came down to normal levels.

The reports on the blood samples taken before treatment was instituted were as follows: There was 35 mg. of sugar in 100 cc. of whole blood, 20.8 mg. of urea nitrogen in 100 cc. of serum and 7.2 mg. of calcium in 100 cc. of serum.

There was 39 mg. of sugar in 100 cc. of whole blood twelve hours after the first clysis of 5 per cent dextrose in isotonic solution of sodium chloride.

The diagnoses entertained at this time were (1) possible intracranial hemorrhage; (2) dehydration; (3) fever due to dehydration or of central origin; (4) hypoglycemia, the cause of which was to be determined; (5) possible congenital cardiac anomaly; (6) jaundice, probably physiologic, and (7) possible tetany of the newborn.

The urine at this time was normal except for a trace of albumin. There was no acetone, diacetic acid or sugar in the urine.

There were 5,750,000 red blood cells and 18,000 white blood cells, with 51 per cent polymorphonuclear cells, 2 per cent eosinophils, 46 per cent lymphocytes and 1 per cent monocytes. The hemoglobin reading was 120.

Both mother and baby were Rh positive. These observations ruled out possible erythroblastosis as the cause of the jaundice. The jaundice rapidly subsided without therapy.

On the third day of life the temperature was 101 F. The infant had repeated bouts of twitchings and cyanosis. The turgor of the skin was poor. The tension of the anterior fontanel remained normal. The upper extremities were mildly spastic and kept flexed at the elbows and the wrists. The lower extremities were also spastic but to a lesser extent. The eyes were staring. The fundi of the eyes, examined at this time, were found to be normal. The cardiac murmur remained as previously described. The abdomen was soft, the lower poles of both kidneys being palpable. Intravenous administration of 5 per cent dextrose in isotonic solution of sodium chloride was begun. Small amounts of diluted whole milk with 5 per cent Dextri-Maltose added were given every four hours, with 5

per cent dextrose solution between feedings. For the next forty-eight hours there were practically no twitchings. The child began to take oral feedings better. The turgor of the skin returned to normal. The child, however, was definitely lethargic. As soon as she became well hydrated the cardiac murmur vanished. There was 25 mg. of sugar per hundred cubic centimeters of blood after forty-eight hours of continuous intravenous administration of dextrose. No determi-

TABLE 1.—*Results of Oral Dextrose Tolerance Test*

Fasting level,	10:40 a. m.: 50 mg.
	11:40 a. m.: 62 mg.
	12:30 p. m.: 41 mg.
	1:00 p. m.: 24 mg.
	2:00 p. m.: 31 mg.

nations of the sugar content of the blood were done while the infusion was running.

The report of the roentgenologic examination of the chest was as follows: "The heart is not particularly enlarged. It is somewhat egg shaped, as is occasionally observed with a patent interventricular septum, but I do not feel that the

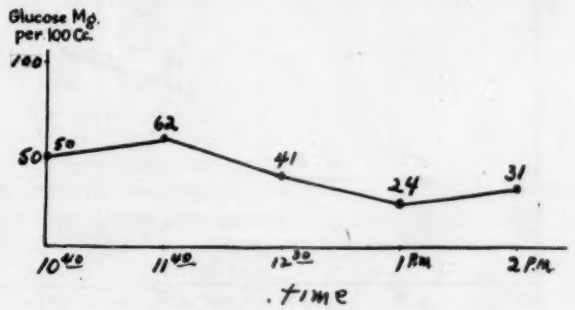

Fig. 1.—Oral dextrose tolerance test (capillary).

roentgenologic evidence is sufficiently distinctive to warrant an unreserved conclusion. The lungs are clear."

The prothrombin time was 12.7 seconds (control, 12.1 seconds). The inorganic phosphorus level was 7.3 mg. per hundred cubic centimeters of serum. The phosphatase was 3.7 units.

TABLE 2.—*Intravenous Dextrose Tolerance Test*

Fasting level,	9:10 a. m.: 43 mg.
	10:10 a. m.: 90 mg.
	10:40 a. m.: 71 mg.
	11:40 a..m.: 44 mg.
	1:40 p. m.: 35 mg.

An oral dextrose tolerance test showed a low curve (plateau type) with sugar levels falling below the initial low fasting level, most likely because of the stimulating effect of the dextrose on production of insulin (fig. 1).

An intravenous dextrose tolerance test showed a rapid withdrawal of the circulating glucose (fig. 2).

A test of the response of blood sugar content to epinephrine showed a curve that was somewhat delayed, but the blood sugar climbed to normal limits thus indicating that glycogenolysis was occurring. This, with the persistent absence of acetone in the urine and the absence of hepatomegaly ruled out von Gierke's disease (fig. 3).

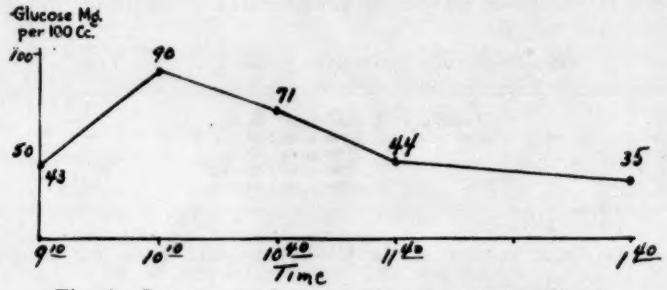

Fig. 2.—Intravenous dextrose tolerance test (capillary).

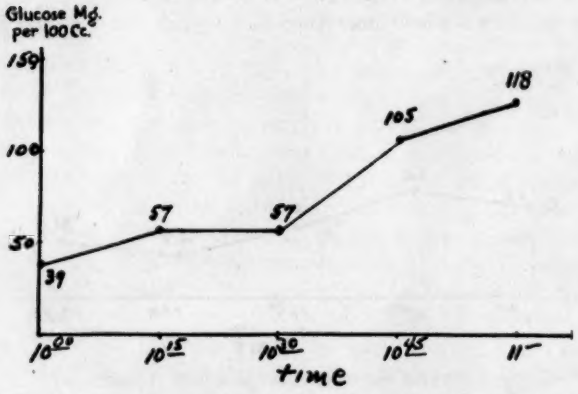

Fig. 3.—Response of blood sugar content to epinephrine.

The child did rather well for a few days, after which the twitchings became almost continuous, with a shrill cerebral type of cry at the height of the convulsive seizures. The child was given phenobarbital and placed in an incubator. Oxygen was administered and clyses were given when deemed necessary.

TABLE 3.—*Response of Blood Sugar Content to Epinephrine*

Fasting level,	10.00 a. m.: 39 mg.
	10:15 a. m.: 57 mg.
	10:30 a. m.: 57 mg.
	10:45 a. m.: 105 mg.
	11:00 a. m.: 118 mg.

Roentgenograms showed a normal sella turcica. The wrists showed no calcified carpal bones.

At no time were there any evidences of intracranial injury. Nevertheless, a subdural aspiration was done to eliminate the possibility of a subdural hematoma. Two subdural punctures were made, one through each coronal suture to the

right and the left of the anterior fontanel. The needles were inserted to a depth of 2 cm. each. Neither fluid nor blood was obtained. A spinal tap done three days earlier was bloody due to trauma.

The patient's general condition deteriorated, with a persistently low level of blood sugar. An exploratory laparotomy was therefore performed when the child was 14 days of age. The child was prepared for operation with a transfusion of whole blood and continuous intravenous infusion. The operation was done with the patient under ether anesthesia. The infant tolerated both the procedure and the anesthesia well. An incision in the upper part of the right rectus abdominis was made. The following is the operative report as recorded by the surgeon: "The stomach, the pylorus, the duodenum, the small bowel and the transverse colon were found to be entirely normal. The adrenal glands, the kidneys and the pelvic organs were normal. The pancreas was clearly visualized and found to be finely lobulated and of light yellowish color; there was neither gross enlargement nor evidence of tumefaction. On the head of the pancreas there was one tiny lobule about the size of a grain of rice which was of the same consistency as the remainder of the gland and did not appear abnormal. This small area was not removed, for it was in the head of the pancreas. It was felt that if this lobule were scooped out there would be danger of opening into the duct of Wirsung with a resulting fistula. The spleen was in its normal position immediately lateral to the tail of the pancreas. In view of the lack of abnormal findings, it was deemed [by the surgeon] inadvisable to attempt removal of any portion of the pancreas merely to obtain a specimen for biopsy. Removal of such a small section, it was felt, would in no way alter the clinical picture. In order to visualize the pancreas it was necessary completely to open and expose the lesser sac."

The child made an uneventful recovery from the operation. The twitchings continued, however. Four days after the operation there was 33 mg. of sugar in 100 cc. of blood and 6.5 mg. of urea nitrogen in 100 cc. of serum.

On Feb. 28, 1945, one week after the operation, an infection of the upper respiratory tract developed, followed three days later by clinical and roentgenologic evidence of pneumonia involving the upper lobe of the right lung. This was treated successfully with oxygen and penicillin. Despite the subsidence of the pneumonia, the child's general condition began to deteriorate. The feedings were taken poorly. The child had repeated twitchings with occasional generalized convulsions preceded by a shrill cry and accompanied by profuse sweating. Intermittent cyanosis was present. There was a bilateral external strabismus with fleeting lateral nystagmus. Examination of the fundi revealed venous engorgement. The disks appeared normal. The infant remained apathetic most of the time. The tension of the anterior fontanel remained normal. The heart sounds were good. The heart was not enlarged and murmurs were not audible.

The child's diet consisted of diluted whole milk with 5 per cent Dextri-Maltose added, 20 drops of percomorph oil, 100 mg. of ascorbic acid and 5 mg. of thiamine chloride twice a day. On February 27 amigen was added to the formula, 1 teaspoonful to each bottle. On March 2 the Dextri-Maltose was decreased to 2 per cent, and 2 per cent Casec was added. Administration of dextrose by mouth was stopped. The amount of Dextri-Maltose was decreased and both Amigen and Casec were added to the formula with the intent of decreasing the insulinogenic sugars and substituting an increased protein intake. No added fat was given because of the infant's tendency toward loose stools.

Supportive measures were resorted to as follows; infusions of plasma, occasional clyses of 5 per cent dextrose in isotinic solution of sodium chloride to

maintain adequate intake of fluid and continuous intravenous administration of Amigen, which the infant tolerated well. The most beneficial effects were obtained with the intravenous administration of amino acids, the modes of action of which can be explained by (1) effect of the amino acids on the general nutrition, (2) slow release of glucose (gluconeogenesis), (3) correction of dehydration and (4) possible beneficial effect of the added chlorides.

Adrenal cortical extract was given, 4 cc. in twenty-four hours. This extract appeared to raise the level of blood sugar to some extent (fig. 4).

TABLE 4.—*Response of Blood Sugar Content to Adrenal Cortical Extract*

Fasting level,	8:35 a. m. Insufficient sample of blood collected
	9:05 a. m.: 59 mg.
	10:25 a. m.: 49 mg.
	10:50 a. m.: 59 mg.
	11:20 a. m.: 68 mg.
	12:20 a. m.: 55 mg.
	1:45 a. m.: 64 mg.

The child's rapid downhill course prevented the trial of increased dosages of the extract. Despite the increased levels of sugar in the blood while the extract was being administered, the twitchings were pronounced. In view of this observation it was felt that the damage to the brain due to the prolonged hypoglycemia was at least in part responsible for the abnormal symptoms.

Studies to prove adrenal insufficiency were to be done. We had tried but failed to obtain the diabetogenic hormone of the anterior lobe of the pituitary. On March 24, at 6 weeks of age, as the child was being prepared for her 9 a. m. feeding, she suddenly became cyanotic and died.

Additional Laboratory Data.—On February 10 there was 7.2 mg. of calcium per hundred cubic centimeters of blood. On February 12 the indirect van den Bergh reaction indicated that there was 10 mg. of bilirubin per hundred cubic

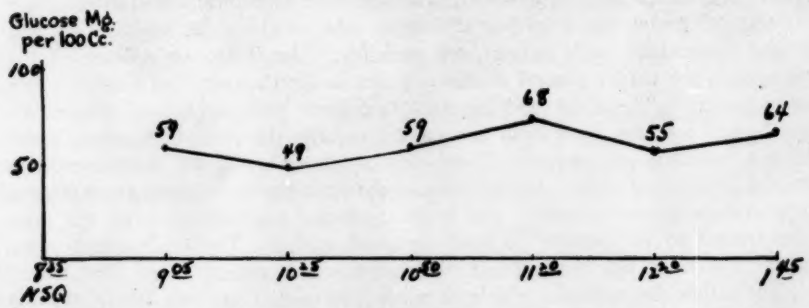

Fig. 4.—Response of blood sugar content to adrenal cortical extract (capillary).

centimeters of blood. On February 16 there was 7.3 mg. of phosphorus, 3.7 units of phosphatase activity, 4.92 Gm. of total protein, 3.20 Gm. of albumin and 1.27 Gm. of globulin per hundred cubic centimeters of blood. The albumin-globulin ratio was 1.9. The indirect van den Bergh reaction indicated that there was 2.4 mg. of bilirubin per hundred cubic centimeters. The cephalin flocculation reaction was negative. On February 19 the carbon dioxide-combining power of the serum was 50.6 volumes per cent. On February 20 there was 342 mg. of chlorides and 9.6 mg. of calcium per hundred cubic centimeters. On February 26 there was 5.31 Gm. of total protein, 6.5 mg. of urea nitrogen, 171 mg.

of total cholesterol and 47.9 mg. of free cholesterol per hundred cubic centimeters. The percentage of free cholesterol was 29.2. On March 5 there was 5.82 Gm. of total protein, 3.49 Gm. of albumin and 1.83 Gm. of globulin. The albumin-globulin ratio was 2.18. There was 1.4 mg. of uric acid, 830 mg. of total lipids, 9.3 mg. of calcium, 6.1 mg. of phosphorus and 5.8 units of phosphatase activity. On March 21 there was 26.1 mg of urea nitrogen.

The mother's sugar tolerance curve was within normal limits.

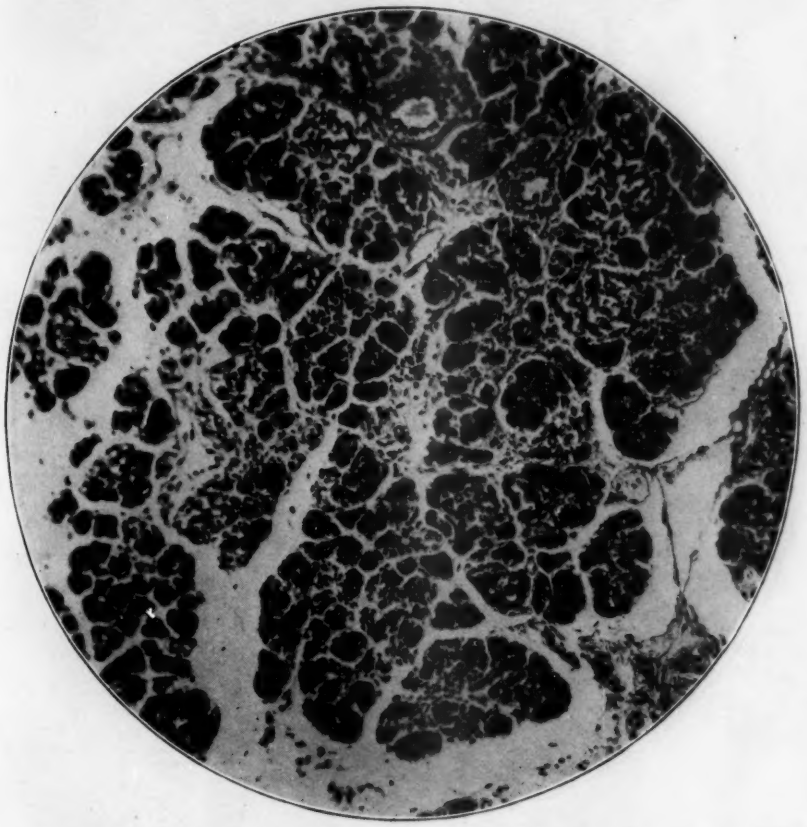

Fig. 5.—Photomicrograph of section from the head of the pancreas, showing many acini and occasional islet structures. Hematoxylin and eosin stain; × 100.

Urine: All specimens of urine were normal except for an occasional faint trace of albumin and occasional white blood cells. At no time was there any acetone, diacetic acid or glucose.

The hemoglobin reading varied from 71 to 120, the red blood cells from 3,580,000 to 5,750,000 and the white blood cells from 18,700 to 27,550, with polymorphonuclear cells from 30 to 51 per cent and lymphocytes from 37 to 62 per cent. Sodium and potassium studies were not done.

Electroencephalographic Studies.—Tracings were made before, during and after administration of dextrose by mouth, during and immediately after administration of dextrose by hypodermoclysis, after a two and one-half day period without

parenteral administration of dextrose or extra dextrose feedings and five hours after a major seizure. The report was as follows: "Neither the resting nor the waking activity nor that recorded during drowsiness and sleep was specifically unusual for a baby of this age. Since the greatest organization of potentials occurred during the period of lowest sugar content in the blood, one would assume that the increase in the cortical activity observed at that time was initiated by the decrease in sugar supplied to the brain. Activity seemed to be within the normal

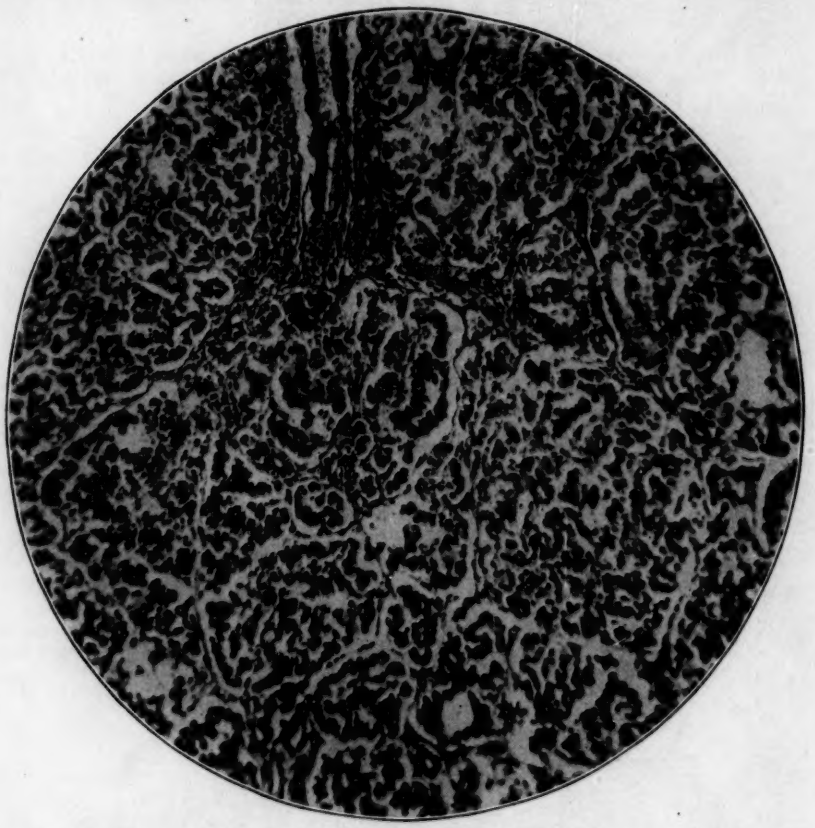

Fig. 6.—Photomicrograph of section from the tail of the pancreas, showing islet structures only. Hematoxylin and eosin stain; × 100.

range for a child 18 to 21 days of age except during periods when the blood sugar was low and convulsive signs were present."

Observations at Autopsy.—Dr. David M. Grayzel performed the autopsy sixteen hours after the child's death. The body was that of a well developed but somewhat poorly nourished white girl. There was no excess fluid in any of the serous cavities of the body.

The heart, the lungs, the liver, the spleen, the kidneys, the adrenal glands and the gallbladder showed nothing of note. They were within normal limits as to weight and size.

The pancreas weighed 13 Gm. The external and the cut surfaces were gray-white and lobular. No nodules were seen anywhere in the pancreas. Sections from the head and the body of the pancreas showed little of note. The lobular architecture was well maintained; the acinar and islet structures were well preserved, and occasional ducts were present, lined with cuboidal cells. Preparations from the tail of the pancreas showed a different picture. Most of the lobules were composed of islet structures of varying size and shape with only occasional

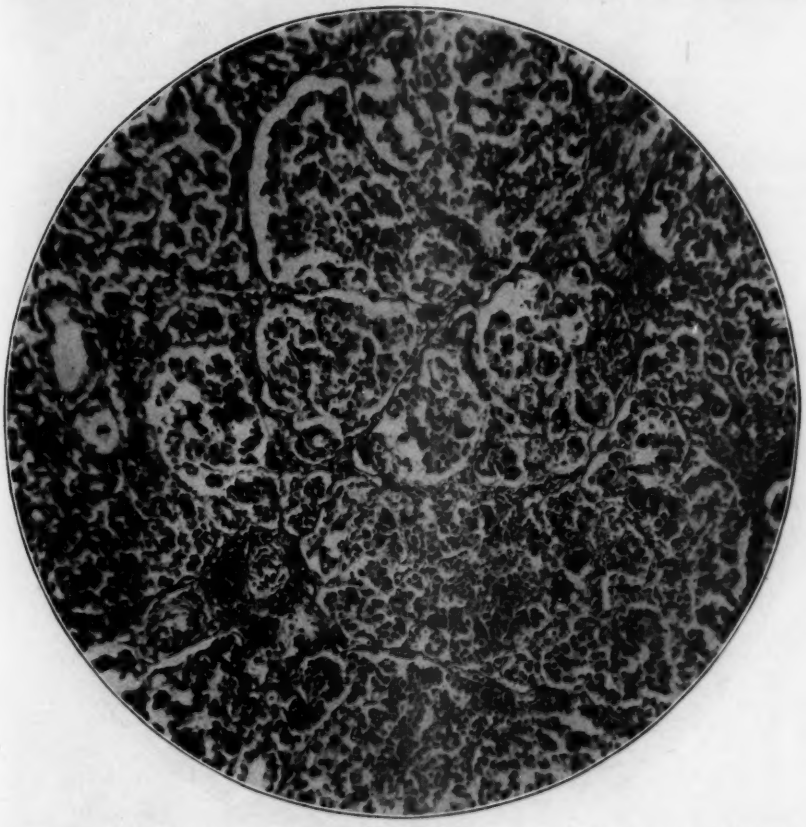

Fig. 7.—Photomicrograph of section from the tail of the pancreas, showing the great preponderance of islet structures with a few, deeper staining, compressed acini. Hematoxylin and eosin stain; × 100.

small and compressed acini present, chiefly at the periphery of the lobules. The supporting stroma was composed of delicate loosely arranged fibrous connective tissue. The cells forming this tumor were strikingly similar to those of normal islands of Langerhans. They were irregularly prismatic and were arranged in anastomosing cords or strands about capillaries. The cytoplasm stained faintly blue and the nuclei varied in size and were round or oval and vesicular. The adenoma reproduced closely the usual islet structures (figs. 5, 6 and 7).

Preparations from various portions of the brain showed striking pictures. The blood vessels were engorged, and there were scattered focal areas of encephalo-

malacia. In sections from the cortex of the brain there were noted an increased cellularity of the tissue and a pronounced diminution of nerve cells. Many cells were in various phases of rhexis. The stroma was loose with scattered focal infiltrations of small round cells. There were throughout great numbers of reacting astrocytes which assumed the form of Nissl plump cells. The nerve cells showed all phases of degeneration from the early stages in which the nuclei were corkscrew and hyperchromatic to complete karyolysis. In the cerebellum, degenerative changes were seen in the Purkinje cell layer (figs. 8, 9 and 10).

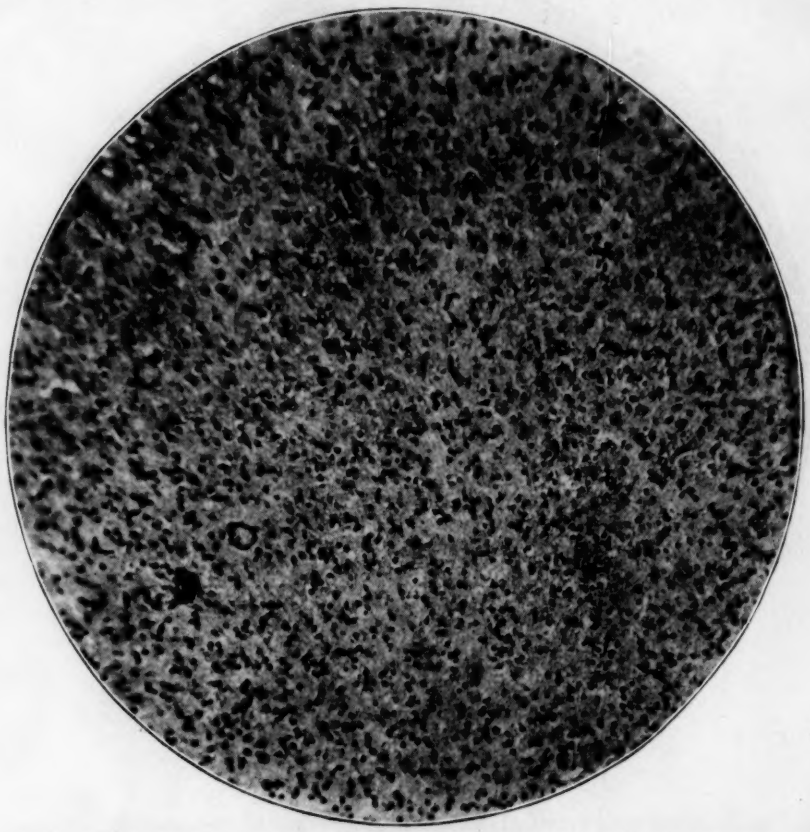

Fig. 8.—Photomicrograph of section from the cortex of the brain, showing gliosis and infiltrations with lymphocytes. Hematoxylin and eosin stain; × 100.

DIAGNOSIS

Routine determinations of sugar content of the blood should be done and followed up in all newborn infants displaying these signs: (*a*) convulsions, the most outstanding sign; (*b*) twitchings; (*c*) hypertonicity; (*d*) irritability; (*e*) somnolence; (*f*) listlessness; (*g*) excessive sweating, especially when associated with cerebral signs; (*h*) poor response to resuscitation; (*i*) intermittent cyanosis, and (*j*) poor feeding. Blood sugar values must be estimated despite the presence of other evidence

which might explain such reactions. The diagnosis of hypoglycemia in the neonatal period is probably most often missed because this condition is not considered. It is of course impossible to state the frequency with which in fatal cases the condition has been incorrectly diagnosed as a cerebral injury at birth because of the history of a prolonged labor

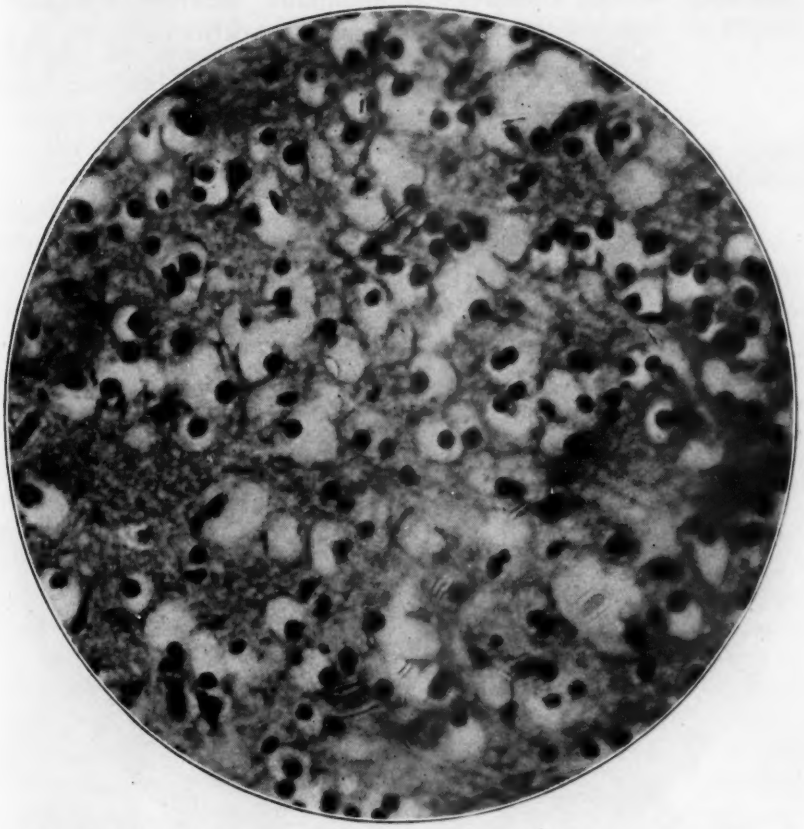

Fig. 9.—Photomicrograph of section from the cortex of the brain, showing cellular infiltration and edema under higher magnification. Hematoxylin and osin stain; × 400.

or an instrumental delivery. The signs of hyperinsulinism are almost entirely due to the effects of the hypoglycemia on the central and the sympathetic nervous system.[21]

21. Cushing, H.: Neurophysiological Mechanisms from a Clinical Standpoint, Lancet **2**:119 and 175, 1930. Wilder, J.: Zur Neurologie und Psychiatrie der hypoglykämischen Zustände, Med. Klin. **26**:616, 1930. Malamud, N., and Grosh, L. C., Jr.: Hyperinsulinism Due to an Islet Cell Adenoma of the Pancreas with Destruction of the Cerebral Cortex: A Preliminary Report, Univ. Hosp. Bull.,

(Footnote continued on next page)

Mild or moderate functional hypoglycemia often occurs in normal newborn infants in the first four to five days of life and more often in premature infants.[20] In these, blood sugars may be found at rather low levels (25 to 60 mg.), usually without symptoms. This condition is most likely due to an incompletely developed carbohydrate-regulatory mechanism, inducing a relative hyperinsulinism. However, it has been thought by some observers that this type of hypoglycemia is due to a

Fig. 10.—Photomicrograph of section from the cortex of the brain, showing degenerative nerve changes. Hematoxylin and eosin stain; × 100.

relatively large number of islands of Langerhans in the pancreas of the newborn infant, but with a rapid decrease in their number during the first year of life there is a gradual increase in the levels of sugar in the

Ann Arbor **3**:70, 1937; Hyperinsulinism and Cerebral Changes: Report of a Case Due to an Islet Cell Adenoma of the Pancreas, Arch. Int. Med. **61**:579 (April) 1938. Moersch, F. P., and Kernohan, J. W.: Hypoglycemia: Neurologic and Neuropathologic Studies, Arch. Neurol. & Psychiat. **39**:242 (Feb.) 1938.

blood. The important fact is that in normal full term or premature babies this hypoglycemia is transitory and usually symptomless and therefore does not present a serious problem. Perhaps, because of the incompletely developed cortex in the newborn infant, with a proportionately low demand for glucose, these babies are more resistant to the effects of hypoglycemia.

In some instances there may be adrenal hemorrhage [22] or tumor,[23] causing destruction of adrenal cortical tissue with resultant lack of substances which inhibit the output of insulin. This condition may also render the cells of the body more sensitive to the effects of insulin.

The syndrome of transient functional hyperinsulinism in infants born to poorly controlled diabetic mothers is well known.[24] Frequently repeated determinations of blood sugar in all such instances are of utmost importance. This condition, although generally readily corrected, must be carefully observed. There is still considerable disagreement as to whether the hypoglycemia is due to simple hyperfunction of normal islets in these infants or to actual hypertrophy and hyperplasia of the islets, although the balance of evidence seems to favor the former view.

Against a diagnosis of a possible hepatogenic causation of the hypoglycemia in our case were the following factors: (*a*) absence of hepatomegaly; (*b*) rapid decline of the bilirubin content of the blood; (*c*) apparently intact glycogenesis and glycogenolysis with a normal response to epinephrine; (*d*) normal free cholesterol; (*e*) normal phosphatase; (*f*) absence of bile in the urine; (*g*) a negative cephalin flocculation reaction; (*h*) absence of ketosis, and (*i*) a normal prothrombin time.

Against a diagnosis of an endocrine cause of the hypoglycemia were the following considerations: (*a*) The pituitary, adrenal, thyroid or thymus glands have never been proved to cause such a pronounced and persistent hypoglycemia as was present in this case. (*b*) The sella turcica was normal. (*c*) The eyegrounds were normal. (*d*) The child's development was normal. (*e*) Total lipids were normal. (*f*) Cholesterol was normal. (*g*) Chlorides were normal.

Against a diagnosis of a primary disorder of the central nervous system were the following factors: (*a*) normal eyegrounds early in the disease, (*b*) negative subdural taps, (*c*) normal roentgenogram of the skull and (*d*) normal tension of the anterior fontanel.

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22. Goldzieher, M. A., and Gordon, M. B.: Hypoglycemia Associated with Adrenal Hemorrhage, Endocrinology **16**:165, 1932.

23. Anderson, H. B.: A Tumor of the Adrenal Gland with Fatal Hypoglycemia, Am. J. M. Sc. **180**:71, 1930.

24. White, P.: Pregnancy Complicating Diabetes, Surg., Gynec. & Obst. **61**: 324, 1935. Randall, L. M., and Rynearson, E. H.: Delivery and Care of the Newborn Infant of the Diabetic Mother, J. A. M. A. **107**:919 (Sept. 19) 1936.

A decrease in the production of hormones by the anterior lobe of the pituitary gland,[25] the adrenal cortex [26] or the thyroid [27] may cause hypoglycemia, usually of only mild or moderate degree, by removing restraint on the production of insulin or by rendering the body cells more sensitive to the action of existing insulin. There have as yet been no definite tests devised to distinguish clearly cases due to true hyperinsulinism from those due to endocrine disturbances. All the clinical features of the particular case must be carefully evaluated in such differentiation. An increased sensitivity to insulin (shown by a test of insulin tolerance [28]) may point to a lack of insulin-inhibiting hormones of the anterior lobe of the pituitary gland or of the adrenal glands.

We have been unable to find any accurate method for the quantitative determination of circulating insulin. If such a method were available a diagnosis of true hyperinsulinism could have been arrived at more directly.

Determinations of calcium levels in the serum should be done for all infants showing disturbances referable to the nervous system to rule out tetany of the newborn. In our case, despite the gradual elevation of the calcium level in the serum from the borderline level of 7.2 mg. to the normal range, the abnormal symptoms persisted.

There is considerable agreement that neither the insulin sensitivity test nor the oral dextrose tolerance tests are of clearcut value in the differential diagnosis of hyperinsulinism. Practically all patients with hypoglycemia demonstrate some sensitivity to insulin, thereby nullifying the usefulness of the test in distinguishing the various types.[29] The

25. Houssay, B. A.: Hypophysis and Metabolism (Dunham Lecture), New England J. Med. **214**:961, 1936. Russell, J. A.: The Relation of the Anterior Pituitary Gland to Carbohydrate Metabolism, Physiol. Rev. **18**:1, 1938.

26. Long, C. N. H.; Katzin, B., and Fry, E. G.: The Adrenal Cortex and Carbohydrate Metabolism, Endocrinology **26**:309, 1940. Lewis, R. A.; Kuhlman, D.; Delbue, C.; Koeuf, C. F., and Thorn, G. W.: The Effect of the Adrenal Cortex on Carbohydrate Metabolism, ibid. **27**:971, 1940. MacBryde, C. M., and de la Balze, F. A.: The Effect on Carbohydrate Metabolism, of Pork Adrenal Cortical Extract, J. A. M. A. **124**:801 (March 18) 1944. Britton, S. W.; Geiling, E. M. K., and Calvery, H. O.: Medulliadrenal Secretion and Carbohydrate Metabolism, Am. J. Physiol. **84**:141, 1928.

27. Burn, J. H., and Marks, H. P.: Relation of the Thyroid Gland to the Action of Insulin, J. Physiol. **82**:195, 1927. Janney, N. W., and Isaacson, V. I.: The Blood Sugar in Thyroid and Other Endocrine Disease: The Significance of Hypoglycemia and the Delayed Blood Sugar Curve, Arch. Int. Med. **22**:160 (Aug.) 1918.

28. The insulin sensitivity test is as follows: Inject ¼ unit of insulin per kilogram of body weight. Either a precipitous drop of the blood sugar level of 30 mg. or more in one hour or sustained low levels indicate increased sensitivity to insulin.

29. Holt, L. E., Jr., and Bridge, E. M.: Hypoglycemia in Early Life, Nebraska M. J. **30**:45, 1945.

results of the oral tests of dextrose tolerance, performed by many observers on many patients with proved insular tumor, have varied so widely that no one type of curve can be distinctly associated with primary hyperinsulinism,[2] In fact, this test may be considered to be more a test of hepatic function than one of pancreatic insular function.[30] In the presence of a flat oral curve, a normal intravenous dextrose tolerance curve may indicate impaired intestinal absorption; also, this test may show a rapid withdrawal of the injected dextrose in cases of hyperinsulinism.

In general, in an infant of a nondiabetic mother manifesting persistent, intractable hypoglycemia with its associated symptoms, and in the absence of signs referable to derangements of hepatic function, endocrine dysfunction or disease of the sympathetic or the central nervous system, a diagnosis of primary hyperinsulinism is justified.

TREATMENT

Conservative dietary management has been found successful in only the cases of rather mild hypoglycemia. The measures employed consist of: (*a*) early formula feedings, (*b*) dextrose water between feedings, (*c*) parenteral administration of dextrose, (*d*) occasional emergency use of epinephrine. Theoretically a diet high in carbohydrate would seem to be indicated, but it is now generally agreed that such a regimen causes increased insulinogenesis which may continue even after complete metabolism of the carbohydrate administered, thereby ultimately aggravating the hypoglycemia. A diet high in protein and moderate with respect to fat, with frequent feedings adjusted to the patient's needs, is the treatment of choice. In our case there was a good response to administration of dextrose only early in its course. Later there was little or no response to the dextrose, and in fact we felt that the infant was hampered by it. The child showed a favorable reaction, however, to Amigen[31] given by mouth and intravenously. Large intakes of protein may be highly beneficial due to the slow release of glucose and the lack of insulinogenic effect of the protein.[32] This also applies to an increased intake of fat, which was not attempted in this case because of the infant's tendency toward loose stools.

When other factors causing persistent or recurring severe hypoglycemia have been reasonably excluded and the diagnosis of primary

30. Whipple, A. O.: Hyperinsulinism in Relation to Pancreatic Tumors, Surgery **16**:289, 1944.

31. Amigen is produced by Mead Johnson & Company.

32. Conn, J. W.: The Advantage of a High Protein Diet in the Treatment of Spontaneous Hypoglycemia, J. Clin. Investigation **15**:673, 1936. Conn, J. W., and Newburgh, L. H.: The Glycemic Response to Isoglucogenic Quantities of Protein and Carbohydrate, ibid. **15**:665, 1936.

hyperinsulinism is the most plausible one, operative intervention is indicated provided that the dietary measures have failed to control the symptoms. Early surgical treatment in the cases of severer disease is essential in order that the excision of the tumor or resection of the pancreas can be done before irreversible damage to the brain ensues and before possibly carcinomatous tumors become inoperable.

The higher centers of the brain are the first and most severely affected by the persistent hypoglycemia. It has been shown by Holmes and Ashford,[33] Lennox [34] and Himwich [35] that lactic acid and its precursor, glucose, are very likely the only source of energy for brain tissue. Reduction of these nutriments in hypoglycemic states readily may cause reversible functional changes, or, if the deprivation is severe or protracted, irreversible pathologic changes may result. Similar changes in the central nervous system have been produced experimentally by administration of excessive insulin to animals in which the degree of changes in the brain was definitely correlated with the intensity and frequency of the convulsions produced. Also, such changes have been found in the brains of persons who have received excessive shock therapy. Even with eventual cure of the hypoglycemia, the existing damage to the brain may result in mental deterioration.

Numerous instances have been reported of the successful removal of adenomas of the islet tissue in cases of intractable hypoglycemia, with restoration of the blood glucose to normal levels. Cases have also been reported in which part of an apparently normal pancreas was removed because no tumor was found at operation. Most of the cases in which there was failure were those in which not enough of the pancreas was resected or in which multiple, active tumors were present or in which a tumor escaped detection because of its location in the head of the pancreas or in its posterior portion.[36] Removal of only two thirds of an apparently normal pancreas may not result in permanent improvement of a hypoglycemic state. Experimentally it has been shown that a diabetic state cannot be induced in the normal dog unless a minimum of 80 per cent of the pancreas is removed.

Graham and Hartmann [37] have reported a case of a year old baby who was operated on for a supposed adenoma of the pancreas. This

33. Holmes, E. G., and Ashford, C. A.: Lactic Acid Oxidation in the Brain, Biochem. J. **24**:1119, 1930.

34. Lennox, W. G.: Cerebral Circulation: The Respiratory Quotient of the Brain and of the Extremities in Man, Arch. Neurol. & Psychiat. **26**:719 (Oct.) 1931.

35. Himwich, H. E., and Nahum, L. H.: Respiratory Quotient of the Brain, Am. J. Physiol. **90**:389, 1929. Himwich, H. E.; Bowman, K. M., and Fazekas, J. F.: Prolonged Coma and Cerebral Metabolism, Arch. Neurol. & Psychiat. **44**:1098 (Nov.) 1940.

36. Wilder.[2] Whipple.[30]

37. Graham, E. A., and Hartmann, A. F.: Subtotal Resection of the Pancreas for Hypoglycemia in an Infant, Surg., Gynec. & Obst. **59**:474, 1934.

not being found, all of the pancreatic tissue was removed save a small portion which was allowed to remain in order to protect the common bile duct. They estimated that between 80 and 90 per cent of the pancreas was removed. There was a prompt improvement in the chronic hypoglycemia without any interference in the general nutrition of the baby or in the acid-base balance of the blood. Careful histologic examination of the entire tissue revealed neither neoplasm nor any demonstrable pathologic condition of the islets or of the islet cells. Other cases of a similar nature have been reported.

Conceivably an excess of the gland might be removed, but the danger of severe hyperinsulinism, which is usually fatal, outweighs the danger of inducing a diabetic state, which can be controlled. Our case bears out the contention that despite the normal appearance and feel of the pancreas at operation excision should be resorted to. Conservatively, at least specimens for biopsy should be taken from various portions of the gland. Ether is the anesthetic of choice, since it tends to raise the level of sugar in the blood.

A secondary operation was considered in our case but because of the pneumonia and the poor general condition of the infant the operative risk appeared to be too great.

Adrenal cortical extract was tried in our case with encouraging results. We had contemplated giving the Kendall "E" fraction of the adrenal cortex, an adrenal steroid, which has a potent effect in raising the level of sugar in the blood, but the child's rapidly downhill course did not permit it.

Under prevailing wartime conditions, we were unable to obtain an extract of the anterior lobe of the pituitary gland containing enough of the diabetogenic hormone to be tried clinically. Experimentally, this hormone has been shown to have a direct effect on the islands of Langerhans, curbing their insulin-producing powers, and if given presistently, it might even cause hydropic degeneration of the islets.[38]

Alloxan.—This substance, the ureide of mesoxalic acid, is a crystalline, faintly pink powder, obtained through the oxidation of the uric acid molecule with nitric acid. Dunn,[39] originally studying its influence on the renal tubules in animals, discovered its early lethal effects, associated not only with tubular damage but with selective necrotic damage to the islets of Langerhans, the acinar tissue being left intact. Some of the animals showed congestion and petechial hemorrhages in the

38. Young, F. G.: Permanent Experimental Diabetes Produced by Pituitary (Anterior Lobe) Injections, Lancet **2**:372, 1937.

39. Dunn, J. S.; Sheehan, H. L., and McLetchie, N. G. B.: Necrosis of Islets of Langerhans Produced Experimentally with Alloxon, Lancet **1**:484, 1943. Dunn, J. S.; Kirkpatrick, J.; McLetchie, N. G., and Telfer, S. V.: Necrosis of the Islets of Langerhans Produced Experimentally, J. Path. & Bact. **55**:245, 1943.

adrenal cortex and the thymus and also cellular changes in the thyroid gland. The lesions in the islets may be due either to direct overestimation of the cells by the drug, resulting in their ultimate exhaustion and death, or to indirect overstimulation through the adrenosympathetic system.

Brunschwig [40] has recently reported on the use of alloxan in the treatment of malignant islet cell tumor, with temporary improvement in symptoms. If this chemical agent is to be an effective therapeutic drug in the treatment of nesidioblastoma in infancy, it must act rapidly to increase the sugar content of the blood before irreversible damage to the brain ensues. The effect must be lasting. It must also be shown conclusively that the toxic and destructive side effects with its temporary or prolonged use do not outweigh the good it might do. Perhaps a compromise therapy might be adopted, the alloxan being used only as a preoperative preparatory agent (like iodine in hyperthyroidism).

We still feel that, to date, early operative removal of the offending islet tissue is the treatment of choice, especially with the newer advances in pancreatic surgical technic.[30] A serious postoperative complication, pneumonia, to which a number of fatalities were attributable in cases mentioned in the literature, is of lesser importance now with the advent of the chemotherapeutic and antibiotic agents. Our patient completely recovered from pneumonia with the use of penicillin despite the severe hypoglycemic state. The fear of the formation of a pancreatic fistula after operation is apparently exaggerated, since in practically all such reported cases there was complete recovery despite this complication.

SUMMARY AND CONCLUSIONS

This case presented a sustained severe hypoglycemia with twitchings and convulsions, showing early a good response to administration of dextrose and injection of epinephrine, with a dextrose tolerance curve demonstrating rapid removal of the circulating glucose. Extrapancreatic causes of hypoglycemia were excluded. The mother was nondiabetic. A clinical diagnosis of primary hyperinsulinism was made, and an exploratory laparotomy was done. Unfortunately neither resection nor biopsy of the pancreas was performed by the surgeon because the gland appeared normal in size, contour and consistency. This error has been stressed. At autopsy typical islet cell adenoma was found.

The tumor in this case was almost microscopic in size, and yet the active hormone secreted by it was either so great in amount or so potent

40. Brunschwig, A.; Allen, J. G.; Owens, F. M., Jr., and Thornton, T. F., Jr.: Alloxan in the Treatment of Insulin Producing Islet Cell Carcinoma of the Pancreas, J. A. M. A. **124**:212 (Jan. 22) 1944. Brunschwig, A., and Allen, J. G.: Attempted Chemotherapy of Islet Cell Carcinoma of the Pancreas, Cancer Research **4**:45, 1944.

in its effect as to cause a fatal outcome despite all the supportive therapy administered.

It is noteworthy that we were able, by supportive treatment, to keep our patient alive for six and one-half weeks despite the severity of the convulsions.

Alloxan therapy is, to date, in the trial stage.

The mother's symptoms, including fatigue, somnolence and excessive sweating during the latter part of gestation, are suggestive of a hypoglycemic effect on the mother by the excessive insulin-secretory activity of the fetal pancreatic adenomatous tissue, the nesidioblastoma probably functioning before delivery.

It is hoped that this report will stimulate an interest in determinations of sugar in the blood in the neonatal period and in pregnant women with symptoms suggestive of hypoglycemia in the last trimester.

Dr. Bejamin Kramer made helpful suggestions and Dr. David M. Grayzel permitted me to use the reports of the autopsy.

661 Wiloby Street (6).

DIPHTHERIA OF THE ESOPHAGUS

A Case Involving Stomach and Tongue

ARCHIBALD L. HOYNE, M.D., CHICAGO

IN PEDIATRIC literature pathologic conditions of the esophagus are probably mentioned less frequently than of any other organ in the human mechanism. From time to time, cases of congenital atresia are reported, and in older children strictures resulting from swallowing lye. But reference to diphtheria invading the gullet is rare indeed. In most textbooks the possibility of diphtheria localizing in the esophagus, or even entering the orifice by extension from the pharynx, is omitted entirely.

Jacobi [1] in his treatise on diphtheria, which was written before Corynebacterium diphtheriae was discovered, discussed diphtheria of the esophagus and the cardiac end of the stomach. However, he stated: "According to Zenker and von Ziemssen the membrane of pharyngeal diphtheria is said to suddenly cease at the entrance into the esophagus." Nevertheless, Jacobi stated that he observed membrane in the upper part of the esophagus over a surface of 1 to 3 cm. in many autopsies in cases of membraneous croup and in 1 instance in which the "diphtheritic deposit" was in the lower part of the esophagus only.

From January 1917, when the Municipal Contagious Disease Hospital was opened, until January 1946, it has admitted 21,765 patients with diphtheria. And from 1912 to 1946 at Cook County Hospital more than 5,000 have been treated. Among the total, about 27,000, nearly all of whom have come under my observation, unusual localizations of diphtheria have included eyes, ears, lower lip, fingers, thigh, foot, abdominal wall, vagina, anus, umbilicus in infants, prepuce after circumcision in infants and, in 1 case, the penis of an uncircumcised boy. The last instance is the only one [2] in which some form of trauma, operative or otherwise, was not a definite factor in the infection.

But perhaps it is not so strange that heretofore diphtheria of the esophagus has been unknown in my experience. Rolleston [3] related in 1939 that Stupka had collected from the literature of the last hundred

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From Municipal Contagious Disease Hospital, Chicago Health Department.

Acknowledgement is made to Dr. Manlio Hernandez Hernandez for the excellent sketch.

1. Jacobi, A.: A Treatise on Diphtheria, New York, William Wood & Company, 1880.

2. Hoyne, A. L., and Levy, A. J.: Diphtheria of the Penis, J. A. M. A. **94:** 1395-1396 (May 3) 1930.

3. Rolleston, J. D., and Ronaldson, G. W.: Acute Infectious Diseases, ed. 3, St. Louis, C. V. Mosby Company, 1940.

years 34 cases of diphtheria of the esophagus, the first of which was reported by Bretonneau and the last 2 by Rolleston. "More than half of Stupka's cases were in children under ten. The upper part of the esophagus was affected in 13, the entire esophagus in 17 and the lower part only in 4." Rolleston also mentioned that Tylecote reported a case of diphtheria of the stomach.

In the following report of an emergency case, observations, examinations, diagnosis, treatment and history are set forth in chronologic order, and not according to the usual and formal entries found on the hospital chart.

REPORT OF CASE

History.—A white girl, 1 month of age (born Jan. 18, 1946) was admitted to Municipal Contagious Disease Hospital at 9:15 p. m., Feb. 20, 1946. The baby was accompanied by her parents. Everything was in readiness for an immediate intubation in the receiving room, as it was known that a patient with diphtheria with difficult breathing was en route to the hospital.

The infant was not robust but was fairly well nourished. She was stuporous, the lips and face were slightly cyanotic and the hands and feet were cold and also cyanotic. The skin over the remainder of the body was pale. There was slight retraction of the abdominal wall and intercostal spaces with inspiration. The respiratory rate was 52; the pulse almost imperceptible and the rectal temperature 101.4 F. Both nostrils were occluded by a smooth, creamy gray membrane, and there was a slight glycerin-like discharge. However, no "diphtheria odor" was detected by me. Breathing was through the mouth. Cervical adenitis was not apparent.

Inspection of the oral cavity revealed a grayish membrane on the tonsils and the posterior wall of the pharynx, where the exudate was of a cheesy consistency. Membrane extended upward like two prongs of a fork from the base onto the dorsum of the tongue. One of these projections at its tip was slightly detached from the tongue, and I removed it for cultural purposes. The baby cried feebly while being handled.

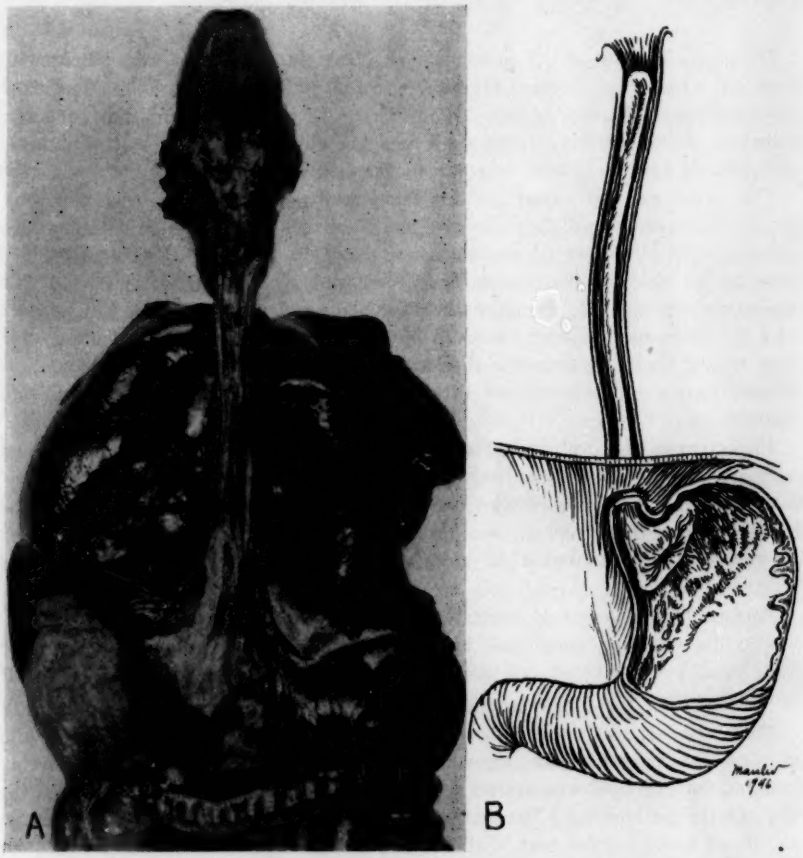
Because of the extremely critical condition of the patient the physical examination in the receiving room was brief. Nose and throat swabs were taken for culturing. A white blood cell count was made, and was found to be 10,000 per cubic millimeter.

Diagnosis.—It was decided that nasal, pharyngeal and tonsillar diphtheria with profound toxemia and bronchopneumonia accounted for the condition. Twenty thousand units of diphtheria antitoxin had been given intramuscularly just before the baby entered the hospital. The patient was taken hurriedly from the receiving room and placed in an oxygen tent. Caffeine and sodium benzoate was administered for stimulation. By midnight the temperature had risen to 104.6 F. This pyrexia was probably due in part to the customary elevation of temperature following administration of diphtheria antitoxin. However, the patient died at 2:23 a. m., February 21, which was approximately five hours after admission.

History Obtained from the Parents.—The baby was normal at birth, breast fed and gaining weight satisfactorily until onset of the present illness. There had been no artificial feeding of any description. On February 16, "a cold" developed and for the next two or three days nursing seemed to be difficult. On February 20, the baby refused the breast and on this date was seen by a physician, who suspected laryngeal diphtheria and recommended hospitalization. Mother,

father and a sibling, a 6 year old girl, were all well and had had no recent illness. The father had diphtheria when a child and the sibling was immunized at 1 year. The mother never had diphtheria. Neither parents nor children had ever been given the Schick test. So far as is known, there were no cases of diphtheria in the neighborhood. Moreover, there has probably never been a time in the history of Chicago when the incidence of diphtheria was at such an extremely low point.

Examination of Cultures.—The nose and throat cultures from the patient were reported positive for diphtheria. But nose and throat cultures taken from



A, fresh specimen, showing diphtheria membrane extending from the base of the tongue downward through the exposed esophagus into the stomach. *B,* sketch of specimen, depicting the lily-like appearance of the diphtheria membrane in the stomach, about the cardiac orifice; above, membrane in the esophagus.

both parents while at the hospital were negative for diphtheria and similar cultures from the child at home were also reported negative. A later test of the culture from the baby demonstrated that the diphtheria organisms were virulent.

Important Observations at the Autopsy.—There was a grayish exudate on the tonsils, the posterior pharyngeal wall and the base of the tongue. The epiglotis

was not involved. From the base of the tongue the membrane extended throughout the esophagus into the stomach. The configuration of the diphtheria membrane could be likened to an Easter lily which had been pulled upward by the stem through the cardiac opening of the stomach to the pharynx. It was as though this imaginary stem were matted onto the base of the tongue and the "flower" remained within the stomach, to which it was adherent, spreading out in oval formation about the cardiac orifice. Thus the diphtheria membrane was continuous and unbroken from the tongue throughout the entire length of the esophagus and extended over about one eighth of the inner surface of the stomach. It was easy to see why the infant had been unable to swallow and had refused to nurse—the exudate caused almost a complete blockage between the pharynx and the stomach. The membrane was less firmly attached at the middle one third than at the two extremities of the esophagus. The upper end of the membrane became separated from the tongue during the autopsy.

When the inner surfaces of the larynx, trachea and bronchi were exposed, there were no signs of any exudate. The mucous membranes of the larynx and trachea were only slightly injected, but there was evidence of bronchopneumonia. The accompanying sketch well illustrates the course and extent of the membrane. The photograph depicts the fresh specimen.

COMMENT

Of all forms of diphtheria, that which involves the esophagus or the stomach is perhaps the most unusual. Facts of further interest in the case reported are the age of the patient, the continuity of the membrane from the base of the tongue to the wall of the stomach and the manner in which the disease was acquired. How a 33 day old baby, breast fed exclusively, contracted diphtheria without known exposure either to an active case or to a carrier was not determined.

The diagnosis of diphtheria of the esophagus or stomach is not likely to be made during the life of the patient. However, a careful examination of the esophagus in cases of severe pharyngeal diphtheria might result in more frequent reports of this condition.

3026 South California Avenue.

News and Comment

GENERAL NEWS

Obligatory Report of Rheumatic Fever.—The Twelfth Panamerican Sanitary Conference, which was held at Caracas, Venezuela, in January 1947, adopted the following motion concerning rheumatic fever:

"Notification of Rheumatic Fever.—The Twelfth Panamerican Sanitary Conference recommends that rheumatic fever be considered as of obligatory report, with the aim of obtaining precise statistics through which exact figures of morbidity of and mortality from the disease might be obtained for the prevention of the consequences and social repercussion of the disease on the health of children and adults."

The vote was presented by the Uruguayan delegation at the request of the Instituto Internacional Americano de Proteccion a la Infancia. The original suggestion came from the Departamento de Salud of the Instituto, with headquarters in Montevideo, Uruguay, and which is under the supervision of Dr. Victor Escardo y Anaya.

During the years from 1945 to 1946 the Department of Health carried out an investigation of rheumatic fever in children in America. This work was well received in the centers of specialization. It was concluded that for as long as rheumatic fever is not considered as an obligatory reportable disease it will not be possible to obtain precise statistics and that therefore the lack will be an obstacle to better results in organizing the crusade against rheumatism.

The motion was unanimously adopted. It is hoped that the various countries will carry out the proper measures to accomplish the aims with the purpose of fighting the terrible disease of rheumatic fever.

Harvard Medical School to Hold Graduate Course in Pediatrics at Massachusetts General Hospital.—Harvard Medical School will hold an intensive two week course, six hours daily, in diagnosis, therapy and prevention of diseases of infants, children and adolescents at the Massachusetts General Hospital, Boston, October 13 to 24, 1947. Discussions based on illustrative cases will cover growth and development, nutrition, endocrinology, metabolic and infectious diseases, allergy, cardiology, surgery, neurology and psychiatry. Further information may be obtained by writing to the following address: Course for Graduates, Harvard Medical School, Boston, Mass.

Fall Examinations of the American Board of Pediatrics.—The American Board of Pediatrics will hold fall examinations on Dec. 5, 6 and 7, 1947, at Dallas, Texas, and on Jan. 9, 10 and 11, 1948, at Philadelphia.

Abstracts from Current Literature

Metabolism; Infant Feeding; Milk and Other Foods

Effects of Inflammation (Turpentine Abscess) on Iron Absorption. P. F. Hahn, W. F. Bale and G. H. Whipple, Proc. Soc. Exp. Biol. & Med. **61**:405 (April) 1946.

Abscesses were produced in 3 dogs which were kept anemic by repeated bleeding and were then given radioactive iron. The intake of iron was much less during the time of the sterile abscess than before and after this period. One animal with splenectomy also had an infection with *Bartonella canis*. These studies indicate that with this inflammatory reaction in the subcutaneous tissues the ability to absorb iron from the gastrointestinal tract is reduced.

Hansen, Galveston, Texas.

Vitamins; Avitaminosis

Lipid Response to Vitamin A Administration: A Possible Test for Vitamin A Deficiency. Hugh W. Josephs, Bull. Johns Hopkins Hosp. **77**:402 (Nov.) 1945.

It had been previously shown that administration of vitamin A to deficient rats caused a marked and prolonged rise in serum lipids. The use of this reaction as a means of recognizing vitamin A deficiency in human beings was tested in this paper. Of a series of infants given high doses of vitamin A the majority showed little or no change in lipid levels. Patients with severe nutritional deficiency showed a definite and prolonged rise, while patients with less severe malnutrition showed a temporary rise. The results suggest that a deficiency of vitamin A causes an increased sensitivity of the serum lipid response to the administration of vitamin A. At this point, however, it can be considered only as suggestive evidence of deficiency and not as a test by which deficiency can be determined.

Lyttle, Los Angeles.

Ascorbic Acid in the Milk of Melbourne Women. Dora Winikoff, M. J. Australia **1**:205 (Feb. 16) 1946.

The ascorbic acid content of breast milk in the Melbourne area ranged from 0.39 to 7.74 mg. per hundred cubic centimeters. The mean value for the whole period of study was 3.67 mg. per hundred cubic centimeters. The mean values for individual months rose slightly from the colostral period, remained constant during the first and second months and gradually fell, reaching the lowest level, of 2.99 mg. per hundred cubic centimeters, during the next month, and then rose again. The results, regrouped according to the calendar month, showed a significant fall in vitamin C content for colostral milk in October and for mature milk in November, which coincided with the shortage of potatoes and fresh vegetables. The histograms revealed that from 50 to 60 per cent of breast-fed babies in the lower and middle income groups did not receive adequate amounts of vitamin C during their first six months of life, as 4 mg. per hundred cubic centimeters is considered the minimum concentration of ascorbic acid in milk necessary for normal nutrition. The author considers that it is urgent to administer some vitamin C supplement even to breast-fed babies as early as the first few weeks of life.

Gonce, Madison, Wis.

Prematurity and Congenital Deformities

AN ANALYSIS OF THE KLIPPEL-FEIL SYNDROME. C. A. ERSKINE, Arch. Path. **41**:269 (March) 1946.

The author reports a case of the Klippel-Feil syndrome. He characterizes the syndrome clinically by shortness of the neck, limitation of movement of the head, and lowering of the hair line, and anatomically by synostosis of two or more cervical vertebrae with flattening and widening of the vertebral bodies. He refers to many cases in the literature in discussing associated regional and distant anomalies. He reviews the theories of pathogenesis which include infections of the patient as a fetus or of the mother during pregnancy, syphilis, dysplastic factors, stability or instability of phylogenetic structures and hereditary factors (citing in support of this theory the occurrences of the syndrome in more than one member of a family). In his review of reported cases of the syndrome he finds the incidence higher in females than in males. He feels that actual numerical reduction of the cervical vertebrae or the presence of spina bifida are not essential features. He supports an embryologic explanation of the anomaly with emphasis on interference in growth and development of regional mesoblastic structures. Such an explanation as this explains the occurrence of the Klippel-Feil syndrome and Sprengel's deformity separately and together on a temporal basis of interference with the growth of cervical mesoblastic structures, the Klippel-Feil syndrome being produced by slightly earlier influences on somatic development.

GEREN, St. Louis.

Acute Contagious Diseases

ADRENAL HEMORRHAGES IN MENINGOCOCCIC SEPSIS. J. SCHWARZ, Arch. Path. **41**:503 (May) 1946.

Dr. Schwarz briefly describes the pathologic changes in the adrenal glands in 5 cases of fulminating sepsis in infants, all of which showed microscopic meningitis and in 2 of which Neisseria intracellularis was identified (from what tissues or body fluids is not stated). He reports medullary hemorrhages as occurring more frequently and extensively than cortical hemorrhages, and found no thrombotic or inflammatory lesions in the adrenal glands. He correlates the presence of large thymuses (15 to 45 Gm.) and a so-called thymolymphatic constitution with adrenal hypoplasia and states that in infants with these changes there is little resistance to "many and heterogenous agents." He feels that the sudden deaths and severe illnesses in fulminating sepsis with adrenal hemorrhages cannot be related to a sudden lack of cortical hormone, since in experiments a complete lack of adrenal glands does not produce acute symptoms for several days. He suggests that the sudden release of a large amount of epinephrine into the blood stream may account for the seriousness of the symptoms in these patients and he awaits further cases for establishing the possible presence of hyperadrenalinemia.

GEREN, St. Louis.

WHOOPING COUGH: PERTUSSIS AGGLUTINATION SKIN TESTS AFTER IMMUNIZATION WITH HEMOPHILUS PERTUSSIS VACCINE. L. W. SAUER and E. D. MARKLEY, J. A. M. A. **131**:967 (July 20) 1946.

The Markley modification of the Kolmer technic for the complement fixation test has been successfully used to test the postvaccination immunity to whooping cough. This test is not practical for general use.

An intradermal test described by Flosdorf, Felton, Bondi and McGuinness and others uses agglutinogen from phase 1 hemophilus pertussis; 0.1 cc. of material made by dissolving 100 units of lyophilized purified agglutinogen in 1 cc. of sterile diluent is injected intradermally. A positive (immune) reaction consists of induration greater than 10 mm. as read either one-half hour or twenty-four hours later. More reactions are positive at twenty-four hours. Erythema is of no immunologic sig-

nificance. The optimum time for testing is four or more months after vaccination. If the induration is 10 mm. or less a stimulating dose of vaccine is indicated. If the reaction is completely negative the full three doses of vaccine are needed.

There is good correlation between the results of this intradermal test and those of the complement fixation test. The data indicate that the intradermal test is a reliable index of vaccine-conferred immunity.

BAIRD, Wauwatosa, Wis.

THE PEDIATRICIAN'S RESPONSIBILITIES IN THE DIAGNOSIS AND TREATMENT OF EARLY POLIOMYELITIS. PHILIP M. STIMSON, J. Pediat. **28**:309 (March) 1946.

In poliomyelitis it is the responsibility of the pediatrician to make the diagnosis, to check the diagnoses of others, to make a practical epidemiologic survey, to initiate the treatment and to coordinate the work of the other specialties. The use of magnesium sulfate gavages is favored.

The diagnosis of bulbar involvement is discussed, as is the proper use of the respirator. The dangers associated with cross infections are noted, and the pediatrician's duty concerning the morale of his patient is emphasized.

KIMBALL, Evanston, Ill.

THE RELATIONSHIP OF INFANTILE PARALYSIS EPIDEMICS TO COMMUNITY RESOURCES IN THE TREATMENT OF PATIENTS. R. PLATO SCHWARTZ, J. Pediat. **28**:313 (March) 1946.

This presentation gives evidence that an area which has had a relatively low incidence of infantile paralysis for nearly three decades may be suddenly confronted with a severe epidemic.

There are in most communities facilities which have been created for the purpose of serving the multiple requirement which becomes evident in such an emergency.

The 1944 epidemic of infantile paralysis in Rochester, N. Y., provided an opportunity to correlate these resources for this purpose. By so doing all major familial and professional difficulties were essentially eliminated as compared with the prevailing situation prior to this correlated effort.

The plan is simple. The resources or their equivalent are common to most communities. The advantage experienced in the 1944 and 1945 epidemics in Rochester, N. Y., is the reason for making this report.

AUTHOR'S ABSTRACT.

THE ROLE OF PHYSICAL MEDICINE IN POLIOMYELITIS. ROBERT L. BENNETT, J. Pediat. **28**:316 (March) 1946.

Physical medicine has an important and well defined role in the treatment of poliomyelitis. It can be considered to have fulfilled its responsibility in the overall program of care if: (1) all available neuromuscular units have been trained to function with the highest possible coordination; (2) all deformities that would limit the most efficient bodily mechanics have been prevented or minimized so far as possible, and (3) the most effective use of any necessary orthopedic apparatus or surgical procedure has been obtained.

AUTHOR'S SUMMARY.

THE PSYCHOLOGIC AND PSYCHIATRIC IMPLICATION OF POLIOMYELITIS. BRONSON CROTHERS and EDITH MEYER, J. Pediat. **28**:324 (March) 1946.

It has long been known that infantile paralysis is a disease that affects various parts of the nervous system. The fact that paralysis is due almost entirely to damage to the spinal cord has left many physicians uninterested in the fact that intellectual and emotional difficulties sometimes occur.

At the Children's Hospital in Boston the authors have been studying the possibility that children need special psychologic study before returning to school. They have found that certain children do not recover from the standpoint of

intellectual endurance for a period of many months. Occasionally they are unable to stand fatigue, and in some instances they are not able to deal with the symbols which are necessary for effective school work.

These conclusions led the authors to the suggestion that some of the difficulties which face persons after attacks of infantile paralysis can be avoided by careful regulation of school pressures in addition to the obvious relief that comes from proper orthopedic care.

It is their feeling that convalescence from infantile paralysis may be just as prolonged in the intellectual and emotional spheres as it is in the motor sphere.

AUTHORS' ABSTRACT.

OBSERVATIONS ON THE 1944 EPIDEMIC OF POLIOMYELITIS IN VIRGINIA. LONSDALE J. ROPER, South. M. J. **39**:344 (April) 1946.

This is a study of 826 cases of poliomyelitis which occurred in Virginia in 1944. It was a particularly dry year, yet the outbreak was the severest on record. The attack rate among the white race was three times that among the Negro race; was higher for males than for females, and decreased with age. The attack rate was higher for women than men in the age group 20 to 29. The mortality rate was 8 per cent. Of the survivors who were followed 65 per cent recovered completely, 14 per cent were only slightly paralyzed, 13 per cent were partially or completely paralyzed in one or more limbs but not totally disabled and 8 per cent were more or less permanently disabled. The severity of the disease seemed to decrease as the outbreak progressed. Eighty-two per cent of the patients were hospitalized. Immediate isolation of the majority of patients did not seem to stop the spread of the disease or its outcome. A discussion of the type of treatment given is not included.

LOGAN, Rochester, Minn.

Acute Infectious Diseases

BED-SIDE AGGLUTINATION TEST WITH WHOLE BLOOD FOR RAPID DIAGNOSIS OF TULAREMIA. RAÚL M. TOVAR, Proc. Soc. Exper. Biol. & Med. **62**:67 (May) 1946.

Whole blood from the ear or finger (amount obtained with 2 mm. loop) is mixed on a slide with an antigen prepared from Pasteurella tularensis (amount carried in a 4 mm. loop), and the slide is moved to and fro and the effect observed in front of a window or bright light. A positive reaction appears within one minute, consisting of a definite separation of colors (blue of the antigen and red of the blood) and the immediate formation of clumps (tendency to form a blue ring at the periphery). The reaction is read as 1, 2, 3 or 4, depending on the time of clumping and size of clumps. The rapid reaction is positive only in cases in which the agglutinating titer of the serum is above 1 to 100. In the negative reactions there is neither separation of color nor clumping of the antigen. The bedside test was positive in 100 per cent of 30 patients whose serum reacted to P. tularensis and in 2 patients whose disease was confirmed as tularemia, and in none of 200 adult control subjects.

HANSEN, Galveston, Texas.

ENTERIC FEVER DUE TO BACTERIUM ENTERITIDIS VAR. BLEGDAM (SALMONELLA BLEGDAM): A SERIES OF FIFTY CASES IN AUSTRALIAN SOLDIERS FROM NEW GUINEA. F. FENNER and A. V. JACKSON, M. J. Australia **1**:313 (March 9) 1946.

Fifty cases of Bacterium enteritidis infection in Australian soldiers are described. The organism was identified as Salmonella enteritidis var. blegdam in 17 cases. The disease is probably endemic throughout New Guinea, New Britain and the Solomon Islands. Clinically, cases fall into two main groups: first, enteric fever (Salmonella fever) of two weeks' duration, and second, an illness which commences in the same way but in which complications develop owing to localization

of infection from the second week onward. Complications include cystitis, epididymo-orchitis, periostitis, perichondritis, cholecystitis, bronchopneumonia, empyema pericarditis and arteritis. The organism can be isolated from the blood in the first and second weeks of the disease, and from the feces and urine in a large number of cases from the second week onward. A slight neutrophilic leukopenia is present in the first and second weeks of the disease. No specific treatment is known.

GONCE, Madison, Wis.

BLOOD VOLUME IN HEALTHY CHILDREN AND IN THOSE CONVALESCING FROM TYPHOID. J. M. VALDES, J. B. SOSA GALLARDO, C. PIANTONI and B. CAPUTTO, Arch. de pediat. d. Uruguay **16**:593 (Oct.) 1945.

Studying the blood volume by the method of Gibson and Evans, the authors found significant differences in a group of 25 children convalescing from typhoid and in a group of 25 apparently healthy children of about the same age. They believe that their results indicate that there is a significant anemic anoxia which explains much of the distressingly slow convalescence in typhoid.

Charts are presented showing measurements of the experimental subjects and the observed differences in hematocrit reading, hemoglobin content, blood volume and plasma volume.

PLATOU, New Orleans.

STERNAL BONE MARROW IN INFANTILE VISCERAL LEISHMANIOSIS. J. FORTEZA BOVER, Rev. espãn. de pediat. **1**:669 (Sept.-Oct.) 1945.

Sternal puncture is recommended instead of puncture of the spleen for the diagnosis of visceral leishmaniasis in infants and children. The procedure is safe as contrasted to puncture of the spleen, which is said to have a mortality of 10 per cent. Furthermore, useful and interesting observations can be made on the reaction of the hemopoietic system to the infection. The author observed a shift to the left in the leukopoietic system with failure of maturation, which is felt to be due to a depressor substance liberated by the enlarged spleen. A similar failure of maturation is seen in the erythropoietic series. In cases of fatal and severe disease there are large numbers of plasma cells seen and the maturation of megalokaryocytes is arrested. The lymphatic system is not affected. These observations are reflected in the anemia, the leukopenia and the thrombopenia of the peripheral blood.

MILLER, Newark, Ohio.

Diseases of Blood, Heart and Blood Vessels and Spleen

EFFECT OF SODIUM SALICYLATE ON THE SEDIMENTATION RATE OF ERYTHROCYTES IN VITRO. F. HOMBURGER, Am. J. M. Sc. **210**:168 (Aug.) 1945.

Sodium salicylate in vitro causes a pronounced reduction of the sedimentation rate of erythrocytes, particularly if it is accelerated.

In fresh plasma this effect takes place at salicylate levels of about 90 mg. per hundred cubic centimeters.

In plasma which has been kept at room temperature for twenty-four hours the effect takes place at levels of 25 to 30 mg. of salicylate per hundred cubic centimeters of plasma.

When salicylate is left in contact with fresh plasma for the same length of time, the slowing of the sedimentation rate occurs at low levels. The standing of plasma at room temperature has an insignificant effect on the sedimentation rate of fresh red blood corpuscles in such plasma.

No demonstrable changes of plasma fibrinogen or red cells are caused by sodium salicylate and changes of the p_H in the plasma do not account for the effect of sodium salicylate on the sedimentation rate. The effect is inherent in the salicylate radical, as sodium benzoate and sodium bicarbonate are ineffective.

HENSKE, Omaha.

EXPERIMENTS ON COMPONENTS A AND B (QUICK) OF PROTHROMBIN. WILLIAM J. ONEAL and CONRAD R. LAM, Am. J. M. Sc. **210**:181 (Aug.) 1945.

The experiments of Quick which suggested the hypothesis that prothrombin consists of at least two components have been corroborated and amplified.

The combination of equal volumes of stored human plasma and plasma from a person given dicumarol produces a mixture with a Quick prothrombin level of from 60 to 70 per cent of normal. The same is true of the corresponding plasmas of the dog.

Fresh human plasma was not superior to stored plasma in such restoration of prothrombin.

The presence of sodium citrate in excess (as in blood bank plasma) did not affect this restorative property.

HENSKE, Omaha.

HEMOLYTIC TRANSFUSION REACTIONS DUE TO THE RH FACTOR: REPORT OF TWO CASES. ARTHUR W. FRISCH, Am. J. M. Sc. **210**:184 (Aug.) 1945.

Two cases of severe reactions following multiple transfusions were found to be due to the Rh factor. In 1 patient an atypical agglutinin conforming to the subtype Rh_1 was demonstrable. In the second the Rh antigen was implicated by discovery of a high titer of "blocking" antibodies in the recipient's serum despite the absence of agglutinins.

HENSKE, Omaha.

TWO CASES OF PERIARTERITIS NODOSA OCCURRING IN THE FIRST MONTH OF LIFE. HARRY A. WILMER, Bull. Johns Hopkins Hosp. **77**:275 (Sept.) 1945.

Two cases of periarteritis in infants are presented. One died at 10 days following a sudden onset of vomiting, pallor, dyspnea and leukocytosis. Umbilical infection was present. The second died at 37 days with symptoms of vomiting, abdominal pain, edema, purpura, fever and leukocytosis. There was a large inflammatory necrotic mass in the right adrenal gland. In both cases there was the typical picture of periarteritis nodosa at autopsy. The clinical diagnosis was not made.

LYTTLE, Los Angeles.

THE SURGICAL TREATMENT OF CHRONIC CONSTRICTIVE PERICARDITIS. GEORGE J. HEUER and H. J. STEWART, New York State J. Med. **45**:993 (May 1) 1945.

The authors present a series of 18 cases in 14 of which there was cure or pronounced improvement by operation. There were no deaths.

The value of surgical treatment in chronic constrictive pericarditis has been proved. Although the condition is relatively uncommon, it usually presents a typical clinical picture which the authors believe is overlooked.

The common clinical manifestations are dyspnea, increase in size of the abdomen due to enlargement of the liver with ascites and edema of the feet and ankles. Physical signs are a nontender, nonpulsating enlargement of the liver with ascites and enlargement of the jugular veins. A paradoxic pulse was present in all the cases.

All physicians should be aware of this disease, which often occurs in youth, since it responds so well to surgical intervention.

THOMPSON, Rochester, N. Y.

PATENT DUCTUS ARTERIOSUS. B. SHALLARD, M. J. Australia **2**:353 (Dec. 1) 1945.

Shallard presents a comprehensive discussion of patent ductus arteriosus and reports 14 cases in which operation was performed. Four of these patients succumbed to the operation, 2 from hemorrhage and 2 from other causes. One died from subsequent infective endocarditis. The patients successfully operated on have been followed for periods varying from two to twenty-one months, and the results are uniformly good. According to the author, a clinical sign not described hitherto is pallor. It was noted in three fourths of the cases and was found not to be related to anemia. A systolic thrill was present in 11 of the cases and in 1 other case

was continuous. The blood pressure readings showed an increased pulse pressure in every case. The patients were predominantly female. In no case was there a history of prenatal maternal rubella. After operation the thrill and murmur disappeared in every instance. The blood pressure readings returned practically to normal The heart became smaller roentgenologically in all cases except 1. The pulmonary artery shadow, when present, failed to disappear after ligation, but was generally smaller.

GONCE, Madison, Wis.

SURGICAL TREATMENT OF PATENT DUCTUS ARTERIOSUS. B. T. EDYE, M. J. Australia **2**:362 (Dec. 1) 1945.

Edye presents a detailed description of the technic of the surgical treatment of patent ductus arteriosus—similar to that described by Gross except for a few minor details.

GONCE, Madison, Wis.

ANAESTHESIA IN CASES OF LIGATION OF PATENT DUCTUS ARTERIOSUS. C. N. PATON, M. J. Australia **2**:362 (Dec. 1) 1945.

Basal narcosis with tribromoethanol, followed by inhalation anesthesia with cyclopropane, was found a satisfactory form of anesthesia in a series of cases of ligation of patent ductus arteriosus. Endotracheal intubation was considered to be advantageous in that it provides an infallible airway, reduces the dead space in which carbon dioxide may accumulate and facilitates the introduction of "controlled respiration" if required, or of artificial respiration or positive pressure. "Controlled respiration" was instituted when possible during the more exacting surgical maneuver.

GONCE, Madison, Wis.

INFECTIOUS MONONUCLEOSIS: SEVERE SUPPURATIVE COMPLICATIONS. JOSÉ M. VALDES and ALBERTO CHATTÁS, Arch. argent. de pediat. **25**:104 (Feb. 19) 1946.

A case of severe staphylococcic sepsis is described in an infant aged 1 year, following infectious mononucleosis cured with penicillin. The authors also mention a similar case cured with penicillin in a child of 14 months.

Attention is called to the fact that infectious mononucleosis can present severe complications during the first two years of life, as much because of the aggregated infections as because the virus may acquire a possibly fatal neurotropic character. They also mention the necessity of making an agglutination test for heterophilic antibodies (Paul-Bunnel test) and the necessity of carrying out active therapy even in advanced complications, especially with transfusions of blood or plasma and with sulfonamide compounds, and the necessity, in case of failure of these means of using penicillin when the presence of organisms sensitive to the drug is proved.

ROJAS, Boston.

PERIARTERITIS NODOSA: A CUTANEOUS AND MUTILATING PROCESS IN A CHILD—CLINICAL AND ANATOMIC OBSERVATIONS. ENRIQUE BALAN, Bol. Soc. cubana de pediat. **17**:293 (Aug.) 1945.

This is the first report of such a case in a child, published in Cuba, and is the one mentioned in a previous article by Galan. The patient was observed over a period of three years and went through seven phases of activity, varying from three weeks to four months and alternating with asymptomatic periods of apparent cure, lasting from twelve days to five months. The salient clinical features were: prolonged fever, at times septic in type, with polyarthritis, abdominal pain, endocarditis, leukocytosis with neutrophilia and eosinophilia; cutaneous eruption such as livido reticularis, purpuric macules, papular infiltrations and necrotizing dermatitis of the abdominal wall, and acroasphyctic syndrome of the fingers, the tongue and the nose with ultimate development of gangrene of the affected parts. Biopsies done in the different phases confirmed the diagnosis and allowed observations of the different stages of the disease.

There are excellent photographs and reproductions of photomicrographs, and detailed clinical studies are reported. This is a real contribution to the study of periarteritis nodosa.

KEITH, Rochester, Minn.

ACUTE HEMOLYTIC CRISIS AFTER PLASMA TRANSFUSIONS IN DYSTROPHIC-TOXIC INFANTS. CONRAD GASSER, Helvet. pædiat. acta **1**:38 (Aug.) 1945.

Acute hemolytic crises, showing the clinical picture of an acute hemolytic anemia (Lederer-Brill) with pallor, icterus without enlargement of the spleen, bilirubinemia and urobilinogenuria was found after several transfusions of group O plasma in 3 dystrophic infants with signs of intoxication. The blood showed hyperchromic anemia, reticulocytosis, leukocytosis and immature elements; erythroblastosis of the bone marrow was found. At the height of the crisis there was microspherocytosis with increased fragility in solutions of sodium chloride and plasma of different blood groups. Recovery is spontaneous or comes after transfusions of blood of the same group.

AUTHOR'S SUMMARY.

IDIOPATHIC MYOCARDITIS IN CHILDHOOD AND ITS DIFFERENTIAL DIAGNOSIS. HANS KELLER, Helvet. pædiat. acta **1**:57 (Aug.) 1945.

Myocarditis of unknown origin in infants is described. The clinical aspects and the pathologic anatomy of 6 cases observed at the Children's Hospital in Zurich are presented. The symptomatology of the disease is reviewed. Differential diagnosis is made in view of another case of possible myocarditis in which there was recovery. The diagnostic difficulties are made evident by the discussion of a case of diffuse rhabdomyomatosis of the heart and another of congenital heart disease with striking improvement of the symptoms.

Out of the group of idiopathic hypertrophies of the heart the author wishes to separate idiopathic interstitial myocarditis. Whether there still remain other forms of so-called idiopathic hypertrophies of the heart is not known at the present time.

AUTHOR'S SUMMARY.

ENDOCARDITIS LENTA IN A NINE YEAR OLD GIRL CORRECTED WITH PROLONGED TREATMENT WITH PENICILLIN. G. FANCONI, Helvet. pædiat. acta **1**:92 (Aug.) 1945.

Two cases of recovery after endocarditis lenta (Streptococcus viridans) in patients with congenital cardiac disease are reported. The treatment of choice consists in intramuscular injections of penicillin given for weeks.

AUTHOR'S SUMMARY.

Diseases of Nose, Throat and Ear

LARYNGEAL EDEMA, MYOCARDITIS AND UNEXPECTED DEATH (EARLY ACUTE LARYNGOTRACHEOBRONCHITIS). OTTO SAPHIR, Am. J. M. Sc. **210**:296 (Sept.) 1945.

The author reports 5 cases of rapidly developed symptoms of obstruction of the upper respiratory tract; the patients succumbed quickly despite tracheotomy. Autopsies disclosed severe laryngeal edema, edema of the epiglottis and subglottic area and acute myocarditis. The edema is interpreted as an early stage of so-called laryngotracheobronchitis. The unexpected death was probably caused by myocarditis. If the attending physician in future instances is aware of this complication, supportive measures might forestall the fatal outcome

HENSKE, Omaha.

SOME FACTS ABOUT STUTTERING. LOREN D. REID, J. Speech Disorders **11**:3, 1946.

The author makes a selective review of the literature concerning stuttering. Stuttering is an astonishingly vague term. "Atomic fission is simple compared with the psychological, endocrinological, biochemical, genetic, and developmental

problems wrapped up in stuttering." Research on stuttering has been going on in a significantly systematic sense for hardly more than twenty years. Many of the observations of early studies conflict with later observations only because investigative methods have been improved. The disorder is complex.

PALMER, Wichita, Kan.

THE RELATIONSHIP BETWEEN VOLUNTARY NON-FLUENCY AND STUTTERING. JAMES HYDE MEISSNER, J. Speech Disorders **11**:13, 1946.

Twenty-four stutterers, 8 females and 16 males, ranging in age from 13 to 22 years, who were undergoing corrective work in the Speech Clinic of the University of Iowa, read three experimental passages in which they were required to read with nonfluency varying percentages of words, and then to proceed immediately to control passages on which no voluntary nonfluency was required (nonfluency or voluntary stuttering consists of repetitive movements of initial consonants and other sounds at a controlled rate—a sort of "fake" stuttering). Conclusions reached were as follows: 1. The frequency of stuttering in the immediate context of words which are produced with voluntary nonfluency is significantly less in passages in which 50 or 25 per cent of the words are nonfluently produced than in passages in which either 0 or 5 per cent of the words are nonfluently spoken voluntarily. 2. This differential effect is not to be observed in the over-all frequency of stuttering in those control passages which immediately followed the experimental passages. 3. Significantly greater amounts of stuttering occur on words which have the larger number of the following attributes: initial consonant, initial position in the sentence, word length greater than five letters, and grammatical function of noun, verb, adjective or adverb. 4. The conclusion concerning stuttering in relation to word weights all applies to errors in producing words with voluntary nonfluency, more such errors occurring on words in the higher weight categories.

PALMER, Wichita, Kan.

A NOTE ON A LINGUA-VELAR RELATIONSHIP. ROBERT HARRINGTON, J. Speech Disorders **11**:25, 1946.

It is possible that in certain phonetic elements there is a proportionate relationship between the elevation of the tongue and the elevation of the velum. Roentgenologic studies to date have not controlled many of the variables in the technic of studying this phenomenon. There is no muscular relationship which would explain it.

PALMER, Wichita, Kan.

INFANT SPEECH VOWEL AND CONSONANT TYPES. HAN PIAO CHEN and ORVIS C. IRWIN, J. Speech Disorders **11**:27, 1946.

Sixteen hundred and twenty-two records of infant speech produced by 95 infants from birth to 2½ years were studied by means of an equation derived from the means of the vowel types and the equation derived from the means of the consonant types. During the first year the mean number of vowel types exceeds the mean number of consonant types. After this the situation is reversed. At 2½ years the infant possesses practically the full complement of vowels and two thirds of the full complement of consonants. It is suggested that the equations may be considered the expressions of the two laws of phoneme type development during infancy.

PALMER, Wichita, Kan.

CLUTTERING. EMIL FROESCHELS, J. Speech Disorders **11**:31, 1946.

In the treatment of cluttering the primary aim is toward the right order in time between the thought phase and the speech phase. Those devices are used which help the patient to control the accuracy, and therefore the tempo, of his articulation. The author has achieved good results with pictorial phonetic script, lip reading and indicating the zone of articulation in reading and conversation.

Every patient treated in this way so far could be cured within three to six months. This experience proves again the part which a rapid speech tempo plays in the development of cluttering.

PALMER, Wichita, Kan.

SIGMATISMUS NASALIS. HELEN HULICK BEEBE, J. Speech Disorders **11**:35, 1946.

The term "sigmatismus nasalis" does not distinguish between the "s" uttered through the nose with a "snoring" component and the "s" uttered through the nose without the "snoring" component. On the basis of a study of 3 cases and other information, it is suggested that sigmatism with the "snoring" component is due to a psychologic factor introduced by the fact that "s" uttered through the nose is hardly audible. It is recommended that speech pathologists adopt appropriate terminology to note this distinction.

PALMER, Wichita, Kan.

THE MASKING EFFECT OF SULFONAMIDE WHEN USED IN THE TREATMENT OF ACUTE OTITIS MEDIA. I. MALCOLM FARQUHARSON, J. Laryng. & Otol. **60**:269 (July) 1945.

Farquharson compares the incidence and the symptoms of mastoiditis in patients who had acute suppurative otitis media and who were treated before sulfonamide compounds came into use with the incidence and the symptoms of mastoiditis in those who received sulfonamide compounds in treatment of suppurative otitis media at the Royal Infirmary in Edinburgh, Scotland. He reports that the incidence of surgical mastoiditis was reduced from 29 to 13 per cent by the use of sulfonamide drugs. He presents a series of illustrative cases with comment. He describes adequately the clinical characteristics of the "masked mastoiditis," stating that the exhibition of a sulfonamide compound is liable to change the ordinary infection of this type into one which is identical with that produced by pneumococci of type III.

He rightly calls attention to the increased incidence of deafness following treatment of otitis media with sulfonamide drugs and to the increasing incidence of chronic suppurative otitis media in patients treated with sulfonamide compounds.

In the discussion on this article, varied opinions are presented about the use of sulfonamide drugs in acute suppurative otitis media. Farquharson states that the sulfonamide drugs should be withheld in certain cases because their effect masks complications. We differ in regard to this, believing that sulfonamide drugs (and penicillin) must be given to control these complications and that the detection of the latter must rest with the diagnostic acumen of the otologist.

LEJEUNE and FARRIOR, New Orleans. [ARCH. OTOLARYNG.]

A REPORT ON SIXTEEN CASES OF SUPRAGLOTTIC OEDEMA. H. MCLORINAN, M. J. Australia **1**:220 (Feb. 16) 1946.

Sixteen patients were admitted to the hospital over a period of eighteen months with a condition of edema of the supraglottic region particularly affecting the epiglottis and the aryepiglottic folds. The clinical picture was one of severe prostration and rapidly developing respiratory obstruction caused by partial occlusion of the glottic opening. There were 2 deaths, 1 of which occurred in the ambulance before the patient's admission to the hospital. In 9 cases tracheotomy was necessary. This is considered to be a life-saving operation in this condition. All patients were treated with sulfonamide compounds, steam tent and oxygen. Penicillin used in some cases seemed to be ineffective. At the time when most of the cases were investigated the literature on the subject was not known, and no special effort was made to cultivate Hemophilus influenzae from the throat or blood. However, 2 of the 3 cases of meningitis, which developed after the initial symptoms of obstruction had been relieved, were due to Hemophilus influenzae type B.

GONCE, Madison, Wis.

Diseases of Lungs, Pleura and Mediastinum

HEMANGIOMA OF THE MEDIASTINUM CAUSING DEATH IN THE NEW BORN. VICTOR W. BERGSTROM, New York State J. Med. **45**:1867 (Sept. 1) 1945.

The author reports 2 cases of fatal mediastinal hemangioma which to his knowledge are the first to be reported in the United States. He believes that the condition is not so rare as would be supposed from the literature.

1. In a healthy-appearing newborn infant symptoms of respiratory difficulty gradually developed, as evidenced by a respiratory grunt, coughing, choking and cyanosis. The symptoms rapidly became worse, and death ensued twenty-six days after birth and fifteen days after the onset. An autopsy revealed a hemangioma of the diaphragm and pericardium, adequately accounting for the symptoms. The onset, development and character of the symptoms are pathognomonic of a progressive mediastinal tumor.

2. A healthy newborn infant showed its first symptoms of black and blue areas in the skin and vomited blood-streaked material twenty-seven days after birth. The symptoms rapidly became severer, with the addition of a slight icteric tinge to the skin, and death followed nine days after the onset and thirty-six days after birth. No symptoms of pressure were observed, probably because of the location of the angioma in the thymus in the upper part of the mediastinum, where there was more room for expansion. An autopsy revealed the cause of death to be hemorrhage due to rupture of the hemangioma into the right pleural cavity.

THOMPSON, Rochester, N. Y.

INHALATION TREATMENT OF BRONCHIAL ASTHMA. ALVAN L. BARACH, New York State J. Med. **46**:1002 (May 1) 1946.

Working in the Department of Medicine, College of Physicians and Surgeons, Columbia University and in the associated Presbyterian Hospital, Barach attempted an appraisal of the various technics of inhalational therapy: (1) oxygen, (2) helium-oxygen mixture, (3) positive pressure with either oxygen or helium-oxygen mixture, (4) filtered air, (5) nebulized solutions of vasoconstrictor or vasodilator drugs, (6) nebulized solutions of penicillin and the sulfonamide compounds and (7) ether anesthesia.

Oxygen relieves functional emphysema and requires no physical effort on the part of the patient. About 10 liters per minute are sufficient to "wash out the carbon dioxide expired." A concentration of from 50 to 70 per cent of oxygen can be obtained. Helium-oxygen mixtures under positive pressure may produce dramatic relief of dyspnea. Filtered air may be of "crucial value" when other measures fail completely. This is especially true when exposure to dust, smoke and fumes gives distress. Epinephrine and neo-synephrine hydrochloride may be useful, especially when there is more emphysema than asthma. However, a point of intolerance may be reached if the patient overdoes hand bulb spraying. Penicillin aerosol is still under experiment. Sore throat and tongue may follow overdosage, but gargling and rinsing mouth and throat after each inhalation tends to prevent this disadvantage. Some patients are allergic to penicillin and therefore should not be subjected to it. In the use of any or all of these technics much depends on the cause of the asthma and a patient's tolerance to the method employed.

VOORHEES, New York. [ARCH. OTOLARYNG.]

Diseases of the Gastrointestinal Tract, Liver and Peritoneum

SALMONELLA APPENDICITIS. A. DANIEL RUBENSTEIN and BEN B. JOHNSON, Am. J. M. Sc. **210**:517 (Oct.) 1945.

The authors summarize the study of Salmonella appendicitis and make the following observations.

When the signs and symptoms of acute appendicitis occur in conjunction with Salmonella infection, a difficult problem in diagnosis is presented. This association was noted in 20 cases, 18 of which came to operation.

While histopathologic examination in 11 of these cases failed to show acute inflammation of the appendix, in 7 instances the report was acute, subacute or gangrenous appendicitis. Review of the operative clinical observations presented no method of differentiating one group from the other.

Of the 20 cases, the 17 which were typed were distributed among five different varieties of Salmonella.

Salmonella typhimurium and Salmonella newport were isolated in cases which showed acute inflammation of the appendix and from those which did not. All 6 cases of Salmonella paratyphi B fell into the category in which involvement of the lymphoid tissue of the appendix or the mesenteric nodes was the most significant pathologic finding.

Although Salmonella infections appear among all age groups, the authors' cases of Salmonellosis associated with appendicitis occurred primarily in children and young adults.

Unexplained persistent postappendectomy fever should raise the question of an underlying Salmonella infection.

Recognition of the basic causation in cases of Salmonella appendicitis will aid in the prevention of secondary infections among contacts in the hospital and at home.

HENSKE, Omaha.

THE EFFECT OF VITAMINS ON ACID FORMATION IN SALIVA. O. E. FANCHER, J. C. CALANDRA and L. S. FOSDICK, J. Dent. Research **23**:23 (Feb.) 1944.

The effect of vitamins on formation of acid in the saliva was determined by measuring the amount of calcium dissolved from powdered human enamel in a limited time by a mixture of saliva, glucose, the vitamin and powdered enamel. It was found that cholesterol, "cerophyl" (a preparation containing a number of vitamins) and possibly thiamine stimulated formation of acid. Synthetic and natural vitamin K both inhibited formation of acid.

BURRILL, Chicago. [ANGLE ORTHODONTIST]

THE EFFECT OF SYNTHETIC VITAMIN K AND RELATED COMPOUNDS ON THE RATE OF ACID FORMATION IN SALIVA. J. C. CALANDRA, O. E. FANCHER and L. S. FOSDICK, J. Dent. Research **23**:31 (Feb.) 1944.

The effect of a number of substances related to synthetic vitamin K on the rate of acid formation in the saliva was determined by measuring the amount of calcium dissolved from powdered human enamel in a limited time by a mixture of saliva, glucose, powdered enamel, and the substance being tested. Quinones and their derivatives and various peroxides were found to have inhibitory effects. Synthetic vitamin K, 2-methyl-1, 4-naphthoquinone, was found equal to any substance and superior to most in its inhibition of acid formation.

BURRILL, Chicago. [ANGLE ORTHODONTIST]

THE EFFECT OF AMYLOLYTIC ENZYMES ON ACID PRODUCTION IN SALIVA. L. S. FOSDICK and G. W. RAPP, J. Dent. Research **23**:85 (April) 1944.

The effect of pancreatic amylase on the formation of acid in saliva was studied by the method described in the foregoing paper. The effect of salivary amylase (ptyalin) was studied by comparing the acid-forming and the ptyalin activities of saliva from different persons. It was found that the pancreatic amylase stimulated formation of acid, though the sugar used, glucose, is not affected by it. High formation of acid and high ptyalin index tended to occur together, but there were many exceptions.

BURRILL, Chicago. [ANGLE ORTHODONTIST]

SOME OBSERVATIONS ON THE ETIOLOGY OF FOREIGN BODIES IN THE ESOPHAGUS. PHILIP READING, J. Laryng. & Otol. **60**:246 (June) 1945.

Of 114 esophagoscopic examinations for suspected foreign bodies, 84 revealed esophageal foreign bodies. No complications or deaths occurred in the series reported. Thirty-three of the patients were children under 13 years of age, while 51 were persons over this age. As to the foreign bodies found in children, coins were the objects in 29 instances while meat bone, toy soldier, curtain ring and jackstone are listed in single cases. Of those found in adults, meat bone and meat bolus were found in 45 instances, while coin, safety pin, needle, beer bottle cap, brooch and denture are listed in single instances.

The author states that the etiologic explanation of esophageal foreign body falls into one of three categories in his cases: 1. The patient knew the foreign body was present in his mouth and swallowed it by accident. 2. The patient deliberately swallowed a foreign body. 3. The patient swallowed a foreign body because he did not know that it was in his mouth. Reading expresses the opinion that the presence of upper dentures greatly enhances the possibility of swallowing a foreign body, as in this series upper dentures were worn by 39 of 40 patients who swallowed bones.

LEJEUNE and STEELE, New Orleans. [ARCH. OTOLARYNG.]

AN EPIDEMIC OF DIARRHOEA CAUSED BY A NEW STRAIN OF THE SALMONELLA GROUP. A. A. FERRIS and R. HERTZBERG, M. J. Australia **2**:368 (Dec. 1) 1945.

An epidemic of mild gastroenteritis occurring among the staff members of an Australian general hospital is described. A total of 29 cases was investigated in the nine day period of the epidemic, and the same Salmonella-like organism was isolated in 26 of them. The name Salmonella atherton is suggested for the organism. Of the 26 Salmonella strains isolated, 8 were detected by direct plating of the stool on desoxycholate citrate agar. The remaining 18 strains were detected only after enrichment with tetrathionate broth. Proteus strains gave surprisingly little trouble, and it was not infrequent to find an almost pure culture of the Salmonella after the plating out of material from the enrichment broth.

GONCE, Madison, Wis.

INTESTINAL DYSBACTERIOSIS IN HEPATOENTEROPATHIES RESULTING FROM DEFICIENCIES OF NUTRITION AND FROM OTHER CAUSES: STUDIES IN CHILDREN AND ADULTS. E. OLIVER PASCUAL, J. ELEIZEGUI and F. ANDOLZ, with collaboration of J. GALAN, A. OLIVER and E. CASTILLO, Rev. españ. de pediat. **1**:779 (Nov.-Dec.) 1945.

This article is more applicable to a journal of gastroenterology than to a journal of pediatrics. It is a study of 40 cases of achlorhydria and 33 cases of "sprue type diarrhea syndrome." Some of these cases are included in both groups. Only 5 of the patients are children. The patients, suffering from a great variety of clinical conditions, showed a failure to utilize fats, increase of fecal organic acids and disturbances in the metabolism of glucose, lipids and protein which is called by the authors "hepatoenteropathy." They also showed a variation from the normal intestinal flora (the paracolon being frequent). This finding is thought to be due in many cases to hypochlorhydria or achlorhydria. Due to the failure of the proper organisms for the formation of vitamin B and C, the patients suffer from deficiencies in these substances.

MILLER, Newark, Ohio.

NEW ANTIDIARRHEAL MEDICATION: CAROB FLOUR. MARC NEYROUD, Ann. pædiat. **166**:113 (March) 1946.

Since 1943, the author and his colleagues have studied in the Hospital for Sick Children of the University of Bern the effect of carob flour on various diarrheal conditions in children beyond the first year of life, and then in infants, too. Spanish authors (F. Ramos and others) first recommended carob flour as an antidyspeptic

agent for children beyond the first year of life. Neyroud and his colleagues were able to confirm its efficacy in enterocolitis, typhoid, bacillary dysentery and celiac disease. But they also had success with carob flour in the treatment of 144 infants with dyspepsia. The carob flour twenty-four hour diet was substituted for the usual tea diet at the beginning of the treatment (decoction in water to 5 per cent for the first half year and 10 per cent for the second half). Stools become abruptly dry, homogeneous, of turflike consistency, often black colored, even sometimes small in size like goat's dung. Then, according to the clinical conditions, they give, with the decoction of carob flour, buttermilk, protein milk (plus 3 per cent Nutromalt [maltose 30 per cent, dextrose 69 per cent and sodium chloride 1 per cent]) sweetened condensed milk or even breast milk, of increasing concentrations (diet of transition). Simultaneously with the transformation of the dyspeptic stools into typical black carob flour stools, they observed an important modification of the stool's flora: reduction of the absolute quantity of bacteria and reappearance of the physiologic intestinal flora. The carob flour disintoxicates the organism and cleans the intestines because of its absorbing substances such as pectins and especially lignin; the tannin of the carob flour is astringent. Children take the carob flour more easily than carrot soup (Elonac). The carob flour represents a considerable progress in the dietetic treatment of infants' and children's diarrhea.

AUTHOR'S SUMMARY.

FAMILIAL CONGENITAL CYSTIC FIBROSIS OF THE PANCREAS WITH BRONCHIECTASIS. H. WISSLER and H. U. ZOLLINGER, Helvet. pædiat. acta, 1945, supp. 1.

The clinical picture of fibrosis of the pancreas can manifest itself in the newborn as meconium ileus, in older infants as indigestion and chronic disease of the respiratory tract and in young children as celiac disease together with chronic bronchitis or pneumonia. Increased excretion of fat in the feces and the reduction or lack of pancreas ferment in the duodenal juice are of great diagnostic value. The prognosis is bad. The disease often occurs in many children of the same parents.

Histologic examination reveals cystic changes in the pancreas which as a rule cannot be detected macroscopically. Suppuration in the lungs (infected bronchiectases) is commonly observed. The changes in the pancreas are caused by embryonic inflammation. The cysts are dilated acini, caused by the interruption of the ducts by proliferating connective tissue. Pancreas fibrosis can easily be differentiated histologically from "congenital cystic pancreas" (malformation).

The bile ducts, the liver, the noninfected bronchiectases and occasionally other organs show chronic inflammation. It is probable that the inflammatory changes in the pancreas, in the bile ducts and the bronchial walls are the result of a single process. The authors believe that the disease is of intrauterine origin, and therefore consider that the cause might have to be sought in the mother.

AUTHORS' SUMMARY.

VERIFICATION OF SUCCESSFUL REPOSITION OF INTUSSUSCEPTION AFTER BARIUM ENEMA. E. WINGE FLENSBORG, Ugesk. f. læger **104**:998 (Sept. 24) 1942.

The author reports on 2 cases of intussusception in children aged 8 months and 21 months respectively. The attempt at reposition by administration of barium enema under roentgenologic control resulted in vomiting of the injected barium emulsion

WALLGREN, Stockholm, Sweden.

Nervous Diseases

PENICILLIN IN THE TREATMENT OF PNEUMOCOCCAL, MENINGOCOCCAL, STREPTOCOCCAL AND STAPHYLOCOCCAL MENINGITIS. WILLIAM L. WHITE, FRANKLIN D. MURPHY, JOHN S. LOCKWOOD and HARRISON F. FLIPPIN, Am. J. M. Sc. **210**:1 (July) 1945.

Seventy-one cases of acute coccic meningitis in which the patients were treated with penicillin are presented. The following conclusions seem justified.

Penicillin was often effective in pneumococcic, meningococcic and streptococcic meningitis after adequate sulfonamide therapy had failed to produce the desired response.

In pneumococcic meningitis the presence of subcranial foci and advanced age were cardinal factors in influencing the mortality rate.

Intrathecal penicillin therapy does not appear harmful. The intracisternal route seems to be the most effective route of intrathecal administration.

Although penicillin administered by the systemic route alone may have a curative effect in selected cases, it seems preferable to supplement systemic administration with intrathecal injections of the drug by the cisternal route.

The superiority of penicillin over other forms of chemotherapy is most clearly demonstrated in staphylococcic meningitis.

It is not unlikely that best results will be obtained through the use of a combination of penicillin and sulfonamide drugs in systemic therapy, and penicillin intrathecally.

HENSKE, Omaha.

A HEREDOFAMILIAL NEUROLOGIC DISEASE, RESEMBLING CHARCOT-MARIE-TOOTH TYPE OF PROGRESSIVE MUSCULAR ATROPHY, IN A CHINESE FAMILY. CALVIN F. KAY and HERBERT S. GASKILL, Am. J. M. Sc. **210**:342 (Sept.) 1945.

The authors describe a case in a Chinese soldier of muscular weakness and atrophy together with sensory abnormalities which began in early childhood. A similar affliction was observed in his mother and 2 of his siblings. The disease is said to have occurred in 11 of 15 descendants of his maternal great grandmother, who suffered from the same disease. While this disease does not fit precisely into any of the known types of heredofamilial neurologic diseases, it most closely approximated the Charcot-Marie-Tooth or neutral type of progressive muscular atrophy.

HENSKE, Omaha.

VASOPARALYSIS AND VASOTHROMBOSIS OF THE BRAIN IN INFANCY AND IN EARLY CHILDHOOD. MARK SCHEINKER, Arch. Neurol. & Psychiat. **55**:216 (March) 1946.

The author reported 3 cases of rapidly fatal disease. One of the patients was 3 years old, and the other 2 were infants. All the patients had signs of intracranial pathologic changes. In each case there were signs of vasoparalysis and vasothrombosis without signs of inflammation.

"Regional peculiarities of vascularization appear to be responsible for the greater vulnerability of the white substance and the relative preservation of the cortex."

This is a valuable article, pointing out that what is often called encephalitis is an entirely different pathologic picture.

BEVERLY, Oak Park, Ill.

THE ELECTRO-ENCEPHALOGRAPHIC LOCALIZATION OF INTRACRANIAL NEOPLASMS. W. A COBB, J. Neurol., Neurosurg. & Psychiat. **7**:96 (July-Oct.) 1944.

In an analysis of the electroencephalograms of 125 patients with intracranial space-occupying lesions, Cobb found that rapidly growing lesions near the free convexity of the cerebrum lend themselves most readily to localization. Thus, about one-half the cerebral tumors were correctly localized, as compared with only 3 of 21 subtentorial tumors and none of the midline or basal tumors. Localization was difficult in the case of parasagittal tumors, especially meningiomas. There was a greater tendency to slowing of the alpha rhythm in cases of tumor than is observed in cases of traumatic injury or of epilepsy. At times a noticeable asymmetry of the alpha rhythm was a useful aid in lateralization. The effect of increased intracranial pressure on the electroencephalogram was not characteristic, the abnormal waves being generalized and usually possessing a frequency of about 2 to 4 per second, irregular rhythm and lower amplitude than that of the alpha rhythm. This electroencephalographic pattern could not be distinguished from that of cortical atrophy, vascular disease or other diffuse condition. There was no direct relation between these changes and the height of intracranial pressure

or the degree of papilledema, but there was some correlation with the state of consciousness. The local effects were not always distinguishable from the generalized effects of high pressure, but as a rule high amplitudes and very slow frequencies were uncommon with the latter. The usual record in a case of tumor was a mixture of slow frequencies.

The "ideal" means of localization is the finding of phase reversal of the slow waves, but not infrequently one must depend rather on their maximum intensity. A 4 to 7 per second frequency band, or theta rhythm, was found to be associated with lesions in the region of the third ventricle. In the opinion of the author, minimal general change may prove to be just as diagnostic in cases of tumor as the presence of a gross dysrhythmia.

MALAMUD, San Francisco. [ARCH. NEUROL. & PSYCHIAT.]

A CASE OF CONGENITAL ATRESIA OF THE FORAMINA OF LUSCHKA AND MAGENDIE: SURGICAL CURE. A. EARL WALKER, J. Neuropath. & Exper. Neurol. **3**:368 (Oct.) 1944.

Walker reports the case of a 20 year old woman who had always had a large head, weakness of the right extremities and unsteady gait. There was a five year history of headaches and fainting spells, usually at the time of the headaches, and in one of these attacks the patient is said to have had clonic movements of the extremities. There were no other abnormal physical or neurologic signs. The correct diagnosis was made clinically on the basis of the roentgenograms of the skull, which revealed that the lateral sinus was conspicuously elevated and the posterior fossa was, accordingly, enormously enlarged. A suboccipital craniectomy was performed and an opening made in the fourth ventricle. Surgical removal of the membrane from the posterior margins of the rhomboid fossa relieved all symptoms, and the patient returned to work. This is the third case to be reported in which the patient survived operation.

GUTTMAN, Philadelphia. [ARCH. NEUROL. & PSYCHIAT.]

A CASE OF PNEUMOCOCCAL MENINGITIS ASSOCIATED WITH CHRONIC MASTOID INFECTION AND COMPLICATED BY MALARIA. J. H. COLEBATCH, M. J. Australia **2**:371 (Dec. 1) 1945.

This case of pneumococcic meningitis in which recovery followed combined penicillin and sulfonamide therapy is reported because penicillin was given intrathecally, apparently without ill effect, in a concentration (2,500 units per cubic centimeter) five times greater than that which is now generally recommended. The total amount of penicillin given was large—70,000 units intrathecally and 900,000 units intramuscularly. The author states that "it is possible that the rather persistent pleocytosis in the cerebrospinal fluid was due to the concentrated penicillin but no harm seemed to result from this feature." However, toward the end of the period of therapy the response to the Queckenstedt test was indefinite, and at the final lumbar puncture completely absent. "This abnormal Queckenstedt response, presumably indicative of intrathecal adhesions, was not present until the second week and did not preclude a satisfactory clinical recovery."

GONCE, Madison, Wis.

THE TREATMENT OF HAEMOPHILUS INFLUENZAE MENINGITIS WITH SULPHONAMIDES IN CONJUNCTION WITH HAEMOPHILUS INFLUENZAE, TYPE B. RABBIT ANTISERUM. E. A. NORTH, H. WILSON and G. ANDERSON, M. J. Australia **1**:215 (Feb. 16) 1946.

In incidence in children Hemophilus influenzae meningitis is usually third to tuberculous and meningococcic meningitis. It is about three times more frequent among children aged under 2 years than in older children. The records of the Children's Hospital, Melbourne, Australia, and of the Royal Alexandra Hospital for Children, Sydney, show that of 157 children of all ages who received no specific treatment, 2 (1.2 per cent) recovered; of 150 who were treated with sulfonamide

compounds 32 (22 per cent) recovered; of 81 who were treated with sulfonamide compounds in conjunction with Hemophilus influenzae, type B, rabbit antiserum, 46 (56.8 per cent) recovered. Recovery under treatment was more frequent with each year of age. Among 9 patients under 2 years to whom the antiserum was given intramuscularly there were 7 recoveries, and among 4 patients over 2 years of age to whom the serum was similarly administered there were 3 recoveries.

GONCE, Madison, Wis.

CEREBRAL ABSCESS OF OTITIC ORIGIN. RAUL VELASCO LETELIER, Rev. otorrinolaring. **5**:236 (Dec.) 1945.

In a survey of 9 cases of cerebral abscess, the author found that in every case the abscess was secondary to chronic suppurative otitis media. The organisms isolated were streptococci, staphylococci and pneumococci. The route of infection in 8 of the cases was by continuity; in the ninth it was by the vascular route. There has not been any association, in any of these cases, with thrombosis of a lateral sinus. The symptom complex was varied and often presented problems in diagnosis. The symptoms can be subdivided in relation to the various stages of formation of the abscess. In its incipiency there is localized encephalitis, which may last for a week or more. Here the symptoms and signs are primarily those associated with either a meningeal or a cerebral infection, such as headaches, high fever, rapid pulse, chills, increase in spinal fluid cell count and the presence of leukocytes in the spinal fluid. The headaches are the most persistent finding. The second stage is that of encapsulation of the abscess, which usually takes about three or four weeks. Here the symptoms are quite different, and the author found that vomiting is extremely common but that it is not of the explosive type, as is usually assumed; it is generally preceded by marked nausea. The headaches are of the typical hemicranial type. Mental phenomena are common, such as somnolence, intellectual dulness and marked indifference and inattention to surroundings. These mental disturbances were noted in 55 per cent of his cases. Bradycardia is common but a very late symptom. Papilledema is not especially common, but the author stresses the importance of the examination of the eyegrounds. Once the abscess is fairly well encapsulated the temperature is not of diagnostic significance, for it usually assumes the lower level and is more or less constant throughout. If the temperature is high or assumes bizarre characteristics, one should suspect other complications, such as meningitis or thrombosis of a lateral sinus. However, the author stresses the postoperative importance of the temperature, for if there is an unexpected rise at that time, one should suspect either interference with the drainage of the abscess or the possibility of further extension of the pathologic process. In addition there are other signs of cerebral localization, such as monoplegia, facial paralysis, diplegia and rarely hemiplegia. The nerve reflexes are usually active or even exaggerated. Nystagmus and conjugate deviation of the eyes were seen in only 2 patients.

Lumbar puncture was done routinely on all patients, but the number of cells in the spinal fluid was not of great prognostic significance. The differential diagnosis of thrombophlebitis and cerebral abscess is sometimes difficult.

Velasco Letelier believes that surgical intervention should be done through the mastoidectomy route. If a fistulous tract is found on exposure of the dura, he follows this to the abscess cavity. When it is absent, he does multiple punctures in various directions until he reaches the mass. He emphasizes the importance of securing ample drainage of the abscess, but this must be done only when the abscess is fairly well encapsulated. The sulfonamide drugs and penicillin are of value only postoperatively. Finally, he believes that the neurosurgeon can be of value in those cases in which the fibrotic character of the capsule interferes with normal function of the brain and produces some secondary symptoms, such as epilepsy, vertigo and migraine. PERSKY, Philadelphia. [ARCH. OTOLARYNG.]

OTITIC MENINGITIS. J. DUCLOS, J. M. CORCUERA and O. IGUALT, Rev. otorrinolaring. **5**:293 (Dec.) 1945.

The authors present 13 cases of otitic meningitis, in 7 of which the meningitis was what they term "sympathetic meningitis," evidenced by signs of meningeal irritation, increase in the spinal fluid pressure, increase in the cellular count up to 420 cells per cubic centimeter and a moderate increase in the serum albumin. However, this type does not show the presence of any particular organism, since it is purely a meningeal reaction to intense toxemia. In the other 6 cases the meningitis was of an acute purulent type, with the presence of pus and organisms. The authors attempted to distinguish between suppurative meningitis which followed acute mastoiditis and that which was associated with the chronic condition. In the former, the symptoms were always of shorter onset, and the temperature was higher and the toxicity much greater. In 4 of the cases of acute mastoiditis pneumococci were found; in 1 case, staphylococci, and in 1, streptococci. Staphylococci were found in every case in which meningitis was associated with chronic mastoiditis. Their operative findings in all cases revealed that the incidence of a pneumatic type of mastoiditis was greatest and that the incidence of a diploic type was second, while a sclerotic type occurred but rarely. At operations their most common finding was coalescent mastoiditis, but there was included among their cases osteitis of the middle portion of the petrous bone, a periphlebitic abscess, phlebitis, a cholesteatoma of the basal petrosa and finally a subdural abscess. Simple mastoidectomy was performed for acute mastoiditis, while radical mastoidectomy was done for chronic mastoiditis. Postoperatively in every case the patient received a sulfonamide drug, preferably sulfadiazine, supplemented with penicillin, which was given both intramuscularly and intraspinally. There was one death in this group of cases. PERSKY, Philadelphia. [ARCH. OTOLARYNG.]

INFLUENZAL MENINGOENCEPHALITIS WITH ACUTE CEREBRAL TREMOR. KONRAD MEIER, Helvet. pædiat. acta **1**:219 (Feb.) 1946.

Two cases of influenzal meningitis—both patients were boys, one 13 months old and the other 3½ years—are discussed. As may be seen in epidemic meningitis, both presented symptoms of encephalitic involvement. Recovery without sequelae occurred following treatment with large quantities of sulfonamide compounds (sulfathiazole and sulfamezathine). The first case with the history of intermittent high fever showed an acute cerebral tremor. The main symptom of Zappert's disease is a rough tremor (shaking tremor) which may follow infectious diseases such as pneumonia, enteritis, measles or chickenpox after a certain time of incubation. The syndrome is usually seen in small children and is more frequently found in boys than in girls. It is thought to be an encephalitis in the form of a neuroallergic reaction. Recovery takes place without sequelae.

As is shown by one of the author's cases there may be a primary form of the acute shaking tremor besides the secondary forms mentioned. In this case a direct action of bacterial toxins or of another poison must be presumed.

AUTHOR'S SUMMARY.

Psychology and Psychiatry

FREQUENCY OF CONVULSIVE DISORDERS IN FEEBLEMINDED. R. W. WAGGONER and J. G. SHEPS, Am. J. Psychiat. **100**:497 (Jan.) 1944.

Waggoner and Sheps maintain that the close relation of convulsive disorders to feeblemindedness is largely due to the presence of many mentally deficient patients in institutions for epileptic patients. The authors therefore studied the incidence of convulsive states in mentally deficient persons. They collected 254 persons with mental deficiency of all types except that associated with congenital syphilis who had lived at least one year and who presented gross or microscopic cerebral lesions. Of this series of 254 patients, 105, or 41.34 per cent, had convulsive attacks. Of patients with the exogenous, or acquired, type of mental

deficiency 51 per cent had convulsive disorders, whereas of patients with the endogenous type 39 per cent were thus afflicted. The authors found no difference in the incidence of convulsive disorders in the various clinical subdivisions of the endogenous type. They stress the infrequency with which convulsions are associated with mongolism. Investigation revealed an incidence of epilepsy in 3.7 per cent of the parents of patients with convulsive disorders and no epilepsy in the parents of those without seizures.

FORSTER, Philadelphia. [ARCH. NEUROL. & PSYCHIAT.]

Diseases of the Genitourinary Tract

WILMS' TUMORS. ARCHIE L. DEAN, New York State J. Med. **45**:1213 (June 1) 1945.

The author presents an excellent, concise discussion of embryonal carcinosarcoma of the kidney (Wilms's tumors).

Of malignant growths in children Wilms's tumors are second in frequency only to tumors of the eye. Whereas in adults renal tumors make up only about 0.5 per cent of all cancers, in children approximately 20 per cent are in the kidney.

The average age of patients when the tumor has been discovered is about 3 years. In common with all other renal tumors, Wilms's tumors produce no symptoms until late in their life history. When symptoms of pain, hematuria, frequency, asthenia and malaise arise, the disease is far advanced. In over 60 per cent of the cases there were no symptoms, and a mass was accidentally felt on abdominal examination.

Immediate excretory urography should be performed to obtain more specific diagnosis. Any properly trained urologist with modern equipment can perform a complete examination without injury to the youngest infant of either sex. Under no circumstances should one incise a Wilms tumor to obtain material for a microscopic examination. This ill chosen operation destroys the capsule and encourages rapid and widespread growth.

The ideal treatment has not been found. The author mentions Ladd's (Ladd, W. E.: *Ann. Surg.* **108**:885, 1938) excellent statistics in which of 60 cases there were 50 per cent survivals of surgical treatment only, after five years, but has been unable to obtain such a percentage of survivals. Using radiation alone in a series of 20 cases he reports that 5 patients are living without evidence of the disease five or more years after treatment. Irradiation is worth while for its palliative effect.

Successful results in this disease depend on early diagnosis and immediate treatment by a competent surgeon or radiologist.

THOMPSON, Rochester, N. Y.

EXTRAVESICAL URETER MALFORMATION IN A SIX MONTH OLD INFANT. H. WILL and H. MARTIN, Helvet. pædiat. acta **1**:31 (Aug.) 1945.

A dislocation of the ureteral orifice into the urethra, combined with doubled ureter on one side, was found in a 6 month old girl. She presented the following characteristic syndrome: persistent voiding, in drops only, of purulent urine from the urethra in presence of an absolutely clear urine in the bladder with practically normal urinalysis. The supernumerary infected ureter was enormously dilated and formed an easily palpable tumor in the fossa iliaca. In view of the serious state of the patient total ureteronephrectomy was the only treatment which was advisable and could successfully be performed.

AUTHORS' SUMMARY.

RENAL TUBERCULOSIS IN CHILDHOOD. WALTER LÜSCHER, Helvet. pædiat. acta **1**:229 (Feb.) 1946.

A report on 21 cases of renal tuberculosis in children is given. Symptoms, course and outcome are described. An interval of three to fifteen years between

the primary complex and the onset of the renal tuberculosis was found in 17 cases. In 16 cases hematogenous spread could be proved by tuberculous residuals elsewhere in the body or by checking the past history. In 12 of the cases it was possible to determine the manner of dissemination. It preceded the appearance of the renal tuberculosis less than three years in 2 cases, between three and five years in 2 other cases and six to ten years in 8 cases.

Symptoms and diagnostic features are practically identical in children and in adults.

Prognosis of renal tuberculosis in childhood is unfavorable. In 12 of the 21 cases the process is bilateral by now, in 4 cases it seems to be unilateral, while in the other 5 cases it is impossible to determine whether the second kidney is really unaffected because of the short time of observation.

Some of the patients have no complaints at all in spite of the severe changes in the bladder found at cystoscopic examination. In these cases the renal tuberculosis was revealed by urinalysis.

AUTHOR'S SUMMARY.

Diseases of the Ductless Glands; Endocrinology

TERATOMA OF PINEAL GLAND WITH CHORIOCARCINOMA AND RHABDOMYOSARCOMA. ROBERT L. GLASS and C. G. CULBERTSON, Arch. Path. **41**:552 (May) 1946.

The authors briefly review the literature on previous reports of similar tumors and mention the controversial origin of teratomatous tumors in the region of the pineal gland. Their case is of a 17 year old youth whose symptoms were of four weeks' duration and could be referred to increased intracranial pressure with additional bilateral convergence of the eyes. He had always been thought to be mentally retarded. Ventriculograms showed symmetric dilatation of the lateral ventricles and dilatation of the anterior half of the third ventricle with a filling defect in the posterior half. An encapsulated tumor mass measuring 33 by 31 by 30 mm. was removed from the region of the pineal gland. The patient died three days later, having had several postoperative attacks of opisthotonos. On section, the tumor showed a cystic portion, a white firm region and a large amount of hemorrhagic, seminecrotic tissue. Microscopically, there were cysts lined with mucus-secreting columnar epithelium and some lined with ciliated epithelium. The white firm region consisted of rhabdomyosarcoma. The hemorrhagic mass contained much necrotic tissue with several small masses of syncytial cells and proliferating Langhans cells. One small area was suggestive of pinealoma. The autopsy showed no remaining tumor. There were no pulmonary metastases. The testes and prostate were not examined microscopically. The photomicrographs are representative sections, apparently, and are well reproduced.

GEREN, St. Louis.

DIABETES IN RELATION TO CERTAIN ORAL AND SYSTEMIC PROBLEMS. PART I: CLINICAL STUDY OF DENTAL CARIES, TOOTH ERUPTION, GINGIVAL CHANGES, GROWTH PHENOMENA AND RELATED OBSERVATIONS IN JUVENILES. D. E. ZISKIN, E. H. SEIGEL and W. C. LOUGHLIN, J. Dent. Research **23**:317 (Oct.) 1944

Except for a tendency toward gingival and peridental trouble, neither diabetes nor the procedures in its control produced any apparent difference in any of the matters studied. The study was carried out in 94 children, of ages ranging from 4 to 19 years. The caries experience (D.M.F.) was estimated from clinical examinations Every pit or fissure which could be caught with an explorer was considered carious. Roentgenograms were available for some of the children but were not used in determining the caries experience. The conclusion, in regard to caries, was that there was no significant reduction in tooth decay in diabetic children.

BURRILL, Chicago. [ANGLE ORTHODONTIST.]

EFFECTS OF CALCIUM DEFICIENCY AND PYRIDOXIN DEFICIENCY ON THYMIC ATROPHY (ACCIDENTAL INVOLUTION). HERBERT C. STOERK, Proc. Soc. Exper. Biol. & Med **62**:90 (May) 1946.

An extensive study with albino rats maintained under various dietary conditions (low proteins, starvation, low calcium, deficiency of vitamin B complex, as well as of thiamine, riboflavin, pantothenic acid and pyridoxin) disclosed a proportional decrease in body weight as a whole and the weight of the thymus gland with two exceptions. In pyridoxin deficiency the amount of deficit in the weight of the thymus was much greater than expected from the obtained deficit in body weight, and in calcium deficiency the opposite effect was observed.

HANSEN, Galveston, Texas.

Diseases of the Muscles, Bones, Joints and Lymph Glands

AMYOTONIA CONGENITA (OPPENHEIM'S DISEASE). EUGENE STRANSKY and LEON V. PECACHE, Ann. pædiat. **166**:163 (March) 1946.

A case of amyotonia congenita is presented. Symptoms and causes of the disease are discussed and the literature surveyed.

AUTHORS' SUMMARY.

PROGRESSIVE INFANTILE MUSCULAR ATROPHY OF THE SPINAL CORD (WERDNIG-HOFFMANN DISEASE) AS A SIMPLE RECESSIVE SUBLETHAL MUTATION ON THE BASIS OF TWENTY-NINE CASES IN FOURTEEN FAMILIES. E. HANHART, Helvet. pædiat acta **1**:110 (Nov.) 1945.

A genetic study is made of 14 families, comprising in all 29 cases of progressive infantile muscular atrophy of the spinal cord (Werdnig-Hoffmann), based on the cases of the disease in the Children's Clinics of Zurich and Berne from 1917 to 1945. Thirteen families were of Swiss and 2 of foreign origin. Werdnig-Hoffmann disease occurs more frequently than was supposed; on the other hand, the real non-progressive congenital myatonia of Oppenheim is rare.

Hereditary transmission is recessive, this being clearly proved by the blood relationship of the parents in 43 per cent of the cases and the appearance of similar manifestations in near collateral kinsmen in 2 families, the parents obviously remaining untouched because the hereditary factor is sublethal.

The considerable recessive surplus noted, similar, for instance, to that of amaurotic idiocy (Tay-Sachs) (proportion of affected to nonaffected persons was 1 to 2 instead of 1 to 3), is partly due to the small number of cases studied and partly to a selection's being mostly observed in hospitals. Furthermore, the abnormal frequency in 10 families of other hereditary diseases (schizophrenia, mental debility and organic nervous diseases such as hereditary tremor) may play a part. This picture of the "family of neuropaths" (Curtius) recalls the action of other recessive hereditary factors (principal gene and accessory genes of Timofeeff-Ressovsky), a less specific action than that of the hereditary factor conditioning the character but which nevertheless favors its manifestation. Of note is the frequency of twins from different ova who die early. The proportion of 18 males to 11 females, i. e., approximately 3 to 2, corresponds to the figures quoted in the literature.

The disease always occurs in the first year of life, sometimes even within the uterus, so that the great frequency of spontaneous abortions in affected sisters renders them suspicious as to further homozygosis.

The course of the disease is definitely progressive. The average length of life was 3 years and 3 months, if the 2 persons with retarded forms of the disease are included, but without these atypical subjects, who reached almost the age of 18, only 13.7 months.

Contrary to what was hitherto supposed, the disease can occur in various forms, since, besides the classical muscular atrophy, Glanzmann has discovered a cervical type. It is doubtful whether rudimentary forms of the disease exist. The absence noted now and then of the patellar reflex and even of the Achilles reflex in parents and siblings of carriers can be explained by their heterozygosis.

The intrafamily variations among brothers and sisters are small, whereas within certain families they are pronounced.

The interfamily variation is rather great. Thus, in 1 of the families only Glanzmann's cervical type occurred.

For every sibling of carriers there exists a 25 per cent risk of contracting the same disease. The more serious the other diseases, the more it is necessary to advise against further reproduction in such families.

AUTHOR'S SUMMARY.

FAMILIAL FRAGILITY OF THE BONES, BLUE SCLERAS and DEAFNESS. HOLGER E. NIELSEN, Nord. med. (Hospitalstid.) **15**:2203 (Aug. 1) 1942.

The author reports on a syndrome with familial fragility of the bones, blue scleras, and deafness which ran through five generations. Another symptom was hypermobility of the joints. The abnormalities were inherited as dominant traits. They occurred in 16 of the 32 members of the family who might possibly have contracted the disease.

WALLGREN, Stockholm, Sweden.

Skin Diseases; Allergy

PLURIORIFICIAL ECTODERMOSIS (FIESINGER-BAADER). ROBERT F. LANDOLT, Helvet. pædiat. acta **1**:246 (Feb.) 1946.

Eight cases of pluriorificial ectodermosis treated at the Children's Hospital in Zurich are discussed.

Widespread, partly pseudomembranous inflammation of the mucous membranes of all orifices of the body (conjunctivitis, stomatitis, balanitis and vulvitis) is characteristic, as well as an extremely polymorphous rash showing more or less the tendency to be vesicular. There are two types: type 1, which affects both the mucous membranes and the skin, and type 2, which affects only the mucous membranes. Between these are intermediary forms with severe alterations of the mucous membranes and only a discrete eruption on the skin. Additional typical symptoms are a high persistent fever and a bad general condition. The blood shows leukocytosis with an increase of the neutrophils and a shift to the left, besides moderate eosinophilia.

In 3 of the cases alterations of the spinal fluid (pleocytosis, increase of the total protein content and a pathologic reaction to the colloidal gold test) were observed. These observations have not hitherto been reported in the literature. One patient died, presenting the symptoms of a meningoencephalitis. In this case the Weil-Felix reaction of the blood proved to be positive.

Differential diagnosis is made between pluriorificial ectodermosis and the classical erythema exudativum multiforme. The disease is explained as a syndrome produced by an allergic reaction of the body to different poisons which as a general rule are difficult to determine. It may sometimes be caused by drugs.

AUTHOR'S SUMMARY.

PLURIORIFICIAL ECTODERMOSIS IN A FOUR WEEK OLD INFANT. ROBERT F. LANDOLT, Helvet. pædiat. acta **1**:263 (Feb.) 1946.

The author reports on a typical case of pluriorificial ectodermosis type I in an infant of 4 weeks. The illness took an extremely severe course. Though feeding of the infant was a difficult problem, complete recovery finally resulted. The reported case shows that the disease is found not only in older children but also in infants in the first trimester.

AUTHOR'S SUMMARY.

Surgery and Orthopedics

LOCAL TREATMENT OF BURNS OF THE SECOND DEGREE WITH MERCUROCHROME. M. GROB, Helvet. pædiat. acta **1**:267 (Feb.) 1946.

1. Treatment of burns of the second degree by coagulation with a 2 per cent aqueous solution of merbromin, which the author and his colleagues have been

using for about seven years in the Children's Hospital in Zurich, Switzerland, is superior to the treatment with tannic acid. The production of a scab by means of merbromin is simplified by the fact that the solution—in contrast to tannin—is always available and that a previous disinfection of the burn is not necessary.

The scabs due to merbromin are thinner and less rigid than those due to tannic acid. Retention of a secretion under the crust may be recognized earlier. In using merbromin it is easier to avoid the infectious complications; e. g., erysipelas, wound scarlet fever and septicemia as seen in about one fourth of the cases in which tannic acid was used.

No toxic manifestations due to the mercury which is contained in organic form in the merbromin have been observed up to now, even in cases in which the drug was applied to large superficial areas.

Burns treated with merbromin and healed after about ten to fourteen days show scars in the best possible condition.

AUTHOR'S SUMMARY.

Teeth and Dentistry

PROPHYLACTIC APPLIANCES IN EARLY CHILDHOOD. AGE OFFER-SPITZ, Am. J. Orthodontics **30**:378 (July) 1944.

Four case reports are given demonstrating the use of a removable vulcanite appliance both as a space maintainer and as a working appliance. The author prefers and has developed such an appliance because of the great saving in time and money which makes this appliance accessible to the greatest number of children in Palestine.

LEWIS, Dayton. [ANGLE ORTHODONTIST]

DOES SCIENTIFIC INVESTIGATION SUPPORT THE EXTRACTION OF TEETH IN ORTHODONTIC THERAPY? ALLAN G. BRODIE, Am. J. Orthodontics **30**:444 (Aug.) 1944

This paper presents certain evidence relative to the various conditions which are held to be correlated with the treatment of malocclusions by extraction.

The first condition discussed was the axial inclination of the lower incisors; it was shown that the inclination of lower incisors is an individual characteristic which shows a great range of variability, a range of 28 degrees for class I cases, 35 degrees for class II, division I, and 42 degrees for class II, division II. Tipping distally of teeth for preparation of "toe hold" anchorage was demonstrated to fail of its objective. The roots come forward as far or farther than the crowns go back. Brodie does not feel that orthodonists are qualified to pass on the beauty of the human face; individual preference is alone concerned.

Two cases were illustrated in which extraction had been resorted to. It was noted that the molars were brought forward to a considerably greater degree than the incisors were carried lingually. The incisors were shown to behave like two-armed levers with their apexes going farther forward than the original position.

It is Brodie's opinion that the extraction problem is reduced to a consideration of just one factor: Is there enough bone to hold the teeth in a normal and stable position following treatment?

LEWIS, Dayton. [ANGLE ORTHODONTIST]

WHAT TYPE OF MALOCCLUSION IS PREVENTABLE? P. C. WILLETT, J. Am. Dent. A. **31**:1066 (Aug.) 1944.

One of the intrinsic causes of malocclusion is a redundancy in the number of teeth, and careful early extraction is often indicated. There is not much to be done about prevention of malocclusion when teeth are missing; there must always be a compromise. When malocclusion is fundamentally hereditary in type, little is accomplished by preventive measures. The so-called "transitional malocclusion" is only a series of steps in the transition from the deciduous to the permanent dentition and should be recognized and not subjected to mechanical interference.

The causes of extrinsic types of malocclusion should be recognized early and removed. The author practices the mechanical treatment of cross bites and poster-occlusion in the deciduous denture. The simplest treatment of neutrocclusion is the slow and steady expansion of the mandible from the lingual.

Any professional person who gives advice regarding childhood dentition should have a thorough knowledge of normal occlusion during various stages of development. Lacking this knowledge, he should refer the patient to some one who is competent to give advice.

BLACK, Berkeley. [ANGLE ORTHODONTIST]

DEVELOPMENT OF THE OCCLUSION OF THE TEETH. CHARLES R. BAKER, J. Am. Dent. A. **31**:1470 (Nov.) 1944.

Malocclusion can be lessened a great deal if the deciduous teeth receive adequate treatment, if injurious influences are eliminated and if there is a normal exchange of deciduous for permanent teeth. As soon as a lower bicuspid fully erupts, the corresponding deciduous upper molar should be removed from the arch. Failure to follow this rule may lead to a pronounced labioversion of the maxillary anterior teeth with a deep overbite. The reduction of mesiodistal diameter by grinding is not recommended.

WYLIE, San Francisco. [ANGLE ORTHODONTIST]

Miscellaneous

PENICILLIN: ITS PRESENT STATUS IN THE TREATMENT OF INFECTIONS. CHESTER S KEEFER, Am. J. M. Sc. **210**:147 (Aug.) 1945.

The author describes the use of penicillin in many of the severe infections and concludes that penicillin has exceeded our highest hopes as a chemotherapeutic agent. It is unquestionably the most effective agent for the treatment of many infections. There is no other known chemical that is so powerful against bacteria and so harmless to the host.

All of this is most extraordinary when one appreciates that 50 mg. will cure the average gonococcic infection, 300 mg. or less is needed for patients with pneumococcic lobar pneumonia, and 3 to 5 mg. will arrest between 50 and 70 per cent of the infections in subacute bacterial endocarditis.

What are needed in the future are effective agents for the similar control of gram-negative bacillary infections and virus infections.

HENSKE, Omaha.

A STUDY OF TYPES OF HYPERSENSITIVITY INDUCED BY PENICILLIN. ADOLPH ROSTENBERG JR. and HENRY WELCH, Am. J. M. Sc. **210**:158 (Aug.) 1945.

Five per cent of 144 persons tested with crystalline penicillin sodium exhibited a positve reaction of the tuberculin type, despite the fact that none of these persons had had any prior contact with penicillin.

Repeated multiple intradermal injections of penicillin sodium cause the development in some persons of reactions of the Arthus type, and some of these also showed a tuberculin type of hypersensitivity.

HENSKE, Omaha.

STREPTOMYCIN: A SUMMARY OF CLINICAL AND EXPERIMENTAL OBSERVATIONS. H. CORWIN HINSHAW and WILLIAM H. FELDMAN, J. Pediat. **28**:269 (March) 1946

Streptomycin possesses the pharmacologic characteristics required of a practical antibacterial agent for treatment of human disease.

The range of efficacy of streptomycin extends the possibility of antibiotic therapy to treatment of several diseases which are not amenable to treatment with other chemotherapeutic agents.

Experimental tuberculosis of guinea pigs may be arrested by prolonged treatment with streptomycin even though the disease has been permitted to become well developed prior to institution of therapy.

A total of 54 patients with different types of clinical tuberculosis have been treated with streptomycin. The results indicate the necessity of much more extensive clinical use of the drug in treatment of tuberculosis on an experimental basis. Present evidence clearly indicates that streptomycin does not exert a rapidly curative effect on clinical tuberculosis, although it does appear to modify the course of the disease in a favorable manner and exert a suppressive effect on previously progressive tuberculosis. At the present time it must not be considered as a substitute for any other form of treatment.

AUTHORS' SUMMARY.

FACTS AND FIGURES IN PEDIATRIC MEDICINE. MARGUERITE F. HALL, J. Pediat. **28**:258 (March) 1946.

Facts and figures of interest to pediatricians are presented. These include: the changes in leading causes of death from 1900 to 1940; the unusual incidence of diphtheria in 1945 in contrast to the trend for the last five years; the risk taken by children in the age brackets in which pediatricians concentrate their efforts with respect to such illnesses as scarlet fever, tuberculosis, measles, poliomyelitis, etc. Attention is given to congenital malformations in infants, injuries at birth and prematurity. Considerable emphasis is placed on rheumatic fever to stimulate individual research: clinical, statistical and epidemiologic.

Knowledge of the elementary basic tools of statistics is indicated as an aid to pediatricians in evaluating their own practice and interpreting the reported experiences of their colleagues as well as for contributing to the advancement of the sum total of knowledge in the entire profession. A prerequisite step to statistical analysis is the collection of good data. Questions are posed: How good is an observation? How often can observed results be found by chance in material of the assumed composition? What estimates can be made from reported observations?

Answers to these questions are given in the statistics of probability, i. e., in the tests for statistical significance. Answers are sought for these questions: What can an observed 100 per cent for 8 patients be expected to yield by chance under similar conditions in comparable samples? What are more likely the true odds that can be expected when the observed odds are 37 to 2, based on 39 cases? How good is the mean blood sugar level based on 5 infants after twenty-four hours of fasting? How significant is the mean change in serum protein with ammonium chloride and low sodium chloride diet for 6 patients? Does chance account for the observed greater efficacy in calf lymph virus over culture virus in accelerating the vaccinal cycle? Answers to these questions are given through the usual tests for statistical significance.

AUTHOR'S ABSTRACT.

NEW DEMOGRAPHIC FACTOR: THE "SURVIVORS." E. JASO, Rev. españ. de pediat. **1**:819 (Nov.-Dec.) 1945.

It is pointed out that a fall or rise in infant mortality shows a good or bad state of sanitation of the infant population while a high or low birth rate shows a good or bad state of the population. The interdependence of these two factors is obvious, and both must be taken into consideration in any conception of the final result obtained.

The author defines "survivors" (S) as the number of babies born per thousand population who continue living one year after their birth. Empirically a value of S is normal between 20 and 25, high between 25 and 30 and low from 15 to 20.

MILLER, Newark, Ohio.

Book Reviews

Cornell Conferences on Therapy. Volume I. Edited by Henry Gold, M.D., and others. Price, $3.25. Pp. 322. New York: The Macmillan Company, 1946.

This book is the outgrowth of conferences inaugurated nine years ago. At that time the Department of Medicine and the Department of Pharmacology of Cornell University Medical College initiated weekly meetings during the school year for the discussion of therapeutic procedures. They were planned to integrate the science of pharmacology and physiology with the practice of therapy. The conferences have been continued to the present time.

Every department of the Medical College and Hospital and visitors and students are invited to participate. At each session a pertinent therapeutic question is discussed. The first part of each hour is devoted to the formal introduction of the subject, and the balance of the time is given over to informal questions, answers and debate.

The proceedings of these conferences appeared in *The Journal of the American Medical Association* from 1937 to 1940 and have been published in the *New York State Journal of Medicine* since 1940. In response to numerous requests, the editors have undertaken the yearly publication of a representative group of conferences.

This book is the first volume, and it contains proceedings on fifteen diversified subjects. These discussions contain material which will be of interest to men in all fields of clinical medicine.

The reviewer feels that all who read this book will find it informative and interesting.

Skin Diseases in Children. By George M. MacKee, M.D., and Anthony Cipollaro, M.D. With contributed chapters. Second edition. Price, $7.50. Pp. 448, with 226 illustrations. New York: Paul B. Hoeber, Inc., 1946.

This is the second edition of this popular text on cutaneous diseases of children. Soon after the first edition was published, it was reprinted in England, and in 1940 it was translated into Spanish and published in Madrid and Barcelona, Spain.

The book is written essentially for the general practitioner, and should be appreciated by the busy pediatrician.

While there are a number of cutaneous diseases peculiar only to infancy and childhood many of the adult dermatoses begin in early life. In this book there has been no attempt at scientific classification, and the various diseases are grouped partly on the basis of etiology, partly on the basis of pathology and partly on the basis of clinical similarity.

Every cutaneous disease peculiar to childhood is described, and, while in some cases the text is short, it is concise and embodies all the characteristic points of the disease. There is no waste of space, treatment is emphasized and most of the treatment outlined is based on the authors' personal experience. Special attention is given to methods of treatment that are suitable for the use of the family physician.

Chapters covering the allergic dermatoses, contagious diseases, congenital cutaneous anomalies and syphilis have been contributed by collaborators with special knowledge of these fields. These are all valuable chapters, but the one that will appeal to the young pediatrician is the one on contagious diseases. Here is an adequate and comprehensive discussion of all the important symptoms of the various contagious diseases, with a good differential diagnosis. Treatment is comprehensive, simple and up-to-date, a feature lacking in most books on dermatology.

The text is simply and clearly written and is easy to read. The book is printed in large, legible type. The illustrations are numerous and excellent. It is a book that should prove of inestimable value to the pediatrician, the dermatologist and the general practitioner.

Acrodina infantil. By A. Ballabriga Aguado, M.D. Price not stated. Pp. 88, with numerous illustrations and tables. Zaragoza, Spain: Revista española de pediatri; volume 2 of monographs, 1946.

This publication is a well organized monograph on erythredema polyneuropathy. The subject is taken up in an orderly fashion to cover all aspects of the disease, the author drawing from extensive reading and 16 cases of his own, seen in Switzerland and Spain. It is of interest that while 243 articles are mentioned in the bibliography from the foreign literature, only 11 are mentioned from Spanish publications. This suggests that the disease must be somewhat rarer in Spain than elsewhere.

In treatment, the author uses "bellergal" (each tablet of which contains 0.1 mg. total alkaloids of belladonna, 0.3 mg. ergotamine tartrate and 2 cg. phenobarbital) together with nicotinic acid and thiamine. He feels that his treatment is effective, although the evidence presented is not entirely convincing, considering the fact that the disease tends to be self limiting.

The monograph is a scholarly review of the subject but fails to throw new light on the problem of erythredema polyneuropathy.

L'Acrodynie infantile. By Maurice Péhu, M.D., and Jean Boucomont, M.D. Price, 60 francs. Pp. 94, with 9 illustrations. Paris, France: Masson & Cie., 1944.

This book is the most intensive and detailed treatise which could be desired. It is certainly highly recommendable for the special student of the subject or for the practitioner who experiences a case and wishes to inform himself as to details of every aspect of erythredema polyneuropathy. It will attract his attention to symptoms and changes which he would not suspect and will stimulate his personal observation and investigation of the case. The details discussed are so minute that one cannot expect any addition, except as new facts are discovered. In the exact bibliography the authors cite the most important publications, especially those of the years after 1937. The organization of the book is according to the customary classification in textbooks, a chapter being devoted to each field, starting with the definition and ending with the therapy. The evaluation of motor disturbances, with discussion of examinations of the spinal fluid and of electroencephalographic data, as described in the literature, is just one of the proofs of the thoroughness of the authors. It seems to be the conviction of the authors that the causative agent is a neurotropic virus. Epidemiologic studies and neurologic symptoms seem to point the way in this direction. Some psychoneurotic and vasomotor disturbances of patients were considered as sequelae. No striking suggestions are made in the chapter on therapeutics, but all angles are discussed. The authors quote often long and enthusiastic statements from the literature, only to invalidate them with one sentence at the end of the chapter. A good example is the remark after the discussion of the "anti-infectious treatment": ". . . The anti-infectious therapy (tonsillectomy, streptococcic antiserum, sulfonamide drugs) is legitimate, but one would have to use it in the beginning of the disease, well before the symptoms permit diagnosis."

Directory of Pediatric Societies *

INTERNATIONAL

International Association of Preventive Pediatrics

President: Prof. S. Monrad, Dronning Louises Børnehospital, Copenhagen, Denmark.
Secretary: Dr. Daniel Oltramare, 15 Rue Lévrier, Geneva, Switzerland.

International Congress of Pediatrics

President: Dr. Henry F. Helmholz, Mayo Clinic, Rochester, Minn.
Secretary-General: Dr. L. Emmett Holt Jr., 477 First Ave., New York 16.
Canadian Committee:
Chairman: Dr. Alan Brown, Hospital for Sick Children, 67 College St., Toronto 2.
Secretary: Dr. S. G. Ross, 1390 Sherbrooke St. W., Montreal.
Place: New York. Time: July 14-17, 1947.

International Congress for the Protection of Infancy

Secretary: Prof. G. B. Allaria, Corso Bramante 29, Torino 120, Italy.

Pan American Congress of Pediatrics

President: Dr. Felix Hurtado, Habana, Cuba.
Place: Mayflower Hotel, Washington, D. C. Time: July 9-12, 1947.

Save the Children International Union

President: Mrs. Gordon Morier.
Secretary: Dr. Georges Thélin, 43 Quai Wilson, Geneva, Switzerland.

FOREIGN

Argentine Pediatric Society of Buenos Aires

President: Dr. Martin Ramón Arana, 1809 Rodriguez Peña, Buenos Aires.
General Secretary: Dr. Alfredo Larguia, Cerrito 1179, Buenos Aires.

Associação Paulista de Medicina, Secção de Pediatrias

President: Dr. Vicente Lara.
First Secretary: Dr. Armando de Arruda Sampaio.
Second Secretary: Dr. Luiz Augusto Monteiro Toledo, Av. Brigadeiro Luiz Antonio 393, 1° Andar, São Paulo, Brazil.
Time: Twelfth of every month, 8:30 p. m.

British Paediatric Association

President: Prof. G. B. Fleming, 13 Lynedoch Crescent, Glasgow.
Joint Secretary: Prof. Alan Moncrieff, Hospital for Sick Children, Great Ormond St., London, W. 1.

Danish Pediatric Society

President: Prof. E. Lenstrup, Copenhagen.
Secretary: Dr. Gjørup, Dronning Louises Børnehospital, Copenhagen.

* Secretaries of societies are requested to furnish the information necessary to make this list complete and to keep it up to date.

Nederlandische Vereeniging voor Kindergeneeskunde

President: Dr. J. L. Keyzer, 114 St. Josephstr., Tilburg.
Secretary: Dr. H. Reerink, 2B Paul Krugerstr., Arnheim.
Place: Children's Hospital or Pediatric Clinic. Time: Three times a year.

Palestine Jewish Medical Association, Section of Physicians of Children's Diseases

President: Prof. L. F. Meyer, 29 Toelsohn St., Tel Aviv.
Secretary: Dr. A. Brünn, 9 Maazestre, Tel Aviv.

Royal Society of Medicine, Section for the Study of Diseases in Children

President: Prof. Norman Capon, 49A Rodney St., Liverpool, England.
Secretary: Dr. J. N. O'Reilly, 46 Harley St., London W. 1, England.
Place: 1 Wimpole St., London. Time: Fourth Friday of each month, 4:15 p. m.

Sociedad Boliviana de Pediatria

President: Dr. Ernesto Trigo Pizarro.
Secretary: Dr. Carlos Ferrufino, Casilla 272, La Paz, Bolivia.
Place: La Paz, Bolivia.

Sociedad Cubana de Pediatria

President: Dr. Teodosio Valledor, Habana.
Secretary: Dr. Carlos Hernandez Miyares, Hospital Nuestra Señora de las Mercedes L y 21, Apartado 2430, Habana.
Place: Cátedra de Clinica Infantil, Hospital Nuestra Señora de las Mercedes y Hospital Municipal de Infancia, Habana. Time: Last Wednesday of every month.

Sociedad Dominicana de Pediatria

President: Dr. Alberto Peguero, Ciudad Trujillo, R.D.
Secretary-Treasurer: Dr. Jaime Jorge, Ciudad Trujillo, R.D.
Place: Children's Ramfis Hospital. Time: 8 p. m., last Thursday of every month.

Sociedad Ecuadoriana de Pediatria

President: Dr. Francisco de Icaza Bustamente.
Secretary: Dr. M. I. Gómez Lince, P. O. Box 693, Guayaquil.

Sociedad Mexicana de Pediatria

President: Dr. Luis Berlanga Berumen, Bucareli No. 85, Altos, Mexico.
Secretary: Dr. Jésus Alvarez de los Cobos, Ignacio Mariscal 124, Mexico.

Sociedad de Pediatría de Córdoba

President: Dr. Juan Francisco Herrera, Córdoba, Argentina.
Secretary: Dr. Bernardo Serebrinsky, Dean Funes 2000, Esq. Ocaña (N.), Córdoba, Argentina.
Place: Comite pro Defenso del Niño, Dean Funes 2000, Córdoba, Argentina. Time: Once a month.

Sociedad de Pediatria del Litoral

President: Dr. Jose E. Celoria, Hospital Centenario, Rosario, Argentina.
Secretary: Dr. Gloria Lovell, Hospital Centenario, Rosario, Argentina.

Sociedad de Pediatría de Santiago de Cuba

President: Dr. Antonio Béguez César, Sagarra 107, Santiago de Cuba.
Secretary: Dra. Susana Texdó Vaillant, Padre Pico 57, Santiago de Cuba.
Place: Colegio Médico. Time: Last Tuesday of every month.

Sociedad Venezolana de Puericultura y Pediatria

President: Dr. Pastor Oropeza, Caracas.
Secretary: Dr. Carlos E. Castillo, Hospital Municipal de Niños, Caracas.
Place: Hospital Municipal de Niños Jose Manuel de los Rios, Caracas.

Société de Pédiatrie de Paris

President: Dr. Leveuf, Paris, France.
Secretary: Dr. Jean Hallé, 10 bis Rue Pré aux Clercs, Paris, France.
Place: Hôpital des Enfants Maladies, 149 Rue de Sèvres. Time: 4:30 p. m., third Thursday of every month.

Swedish Medical Society, Section for Pediatrics and School Hygiene

President: Prof. Arvid Wallgren, 53 Strandvägen, Stockholm.
Secretary: Dr. Henning Magnusson, 58 Odengatan, Stockholm.
Place: Various clinics and hospitals in Stockholm and Uppsala. Time: Second Friday of each month (except summer).

Uruguayan Society of Pediatrics

President: Dr. Jose Bonaba, Montevideo.
Secretary: Dr. Héctor Fossatti, Durazno 1882, Montevideo.
Place: Club Medico del Uruguay, Avenida Agraciado 1464 (Piso 13), Montevideo.

NATIONAL

American Medical Association, Scientific Assembly, Section on Pediatrics

Chairman: Dr. Oscar Reiss, 2200 W. 3d St., Los Angeles.
Secretary: Dr. Margaret Mary Nicholson, 1801 Eye St. N. W., Washington, D. C.
Place: Chicago. Time: June 21-25, 1948.

American Academy of Pediatrics

President: Dr. Jay I. Durand, 515 Cobb Bldg., Seattle, Wash.
Secretary: Dr. Clifford G. Grulee, 636 Church St., Evanston, Ill.

American Hospital Association, Massachusetts Hospital Association

Chairman: Dr. Frank Wing, Boston.
Secretary: Dr. W. Franklin Wood, McLean Hospital, Waverly 79, Mass.

American Pediatric Society

President: Dr. Harold K. Faber, 2361 Clay St., San Francisco.
Secretary-Treasurer: Dr. Henry G. Poncher, 1819 W. Polk St., Chicago 12.

Canadian Society for the Study of Diseases of Children

President: Dr. Alan Ross, 1414 Drummund St., Montreal.
Secretary-Treasurer: Dr. R. L. Denton, 3534 Ontario Ave., Montreal.

Society for Pediatric Research

President: Dr. Donovan J. McCune, 3975 Broadway, New York.
Secretary: Dr. Robert Ward, Bellevue Hospital, New York 16.

SECTIONAL

Intermountain Pediatric Society

President: Dr. Wesley H. Anderson, 2404 Washington Blvd., Ogden, Utah.
Secretary-Treasurer: Dr. F. M. Kriete, State Capitol, Salt Lake City.
Place: Salt Lake City General Hospital. Time: First Thursday of each month, 8 p. m.

New England Pediatric Society

President: Dr. James Marvin Baty, 1101 Beacon St., Brookline, Mass.
Secretary-Treasurer: Dr. Charles D. May, 300 Longwood Ave., Boston.
Place: Boston Medical Library. Time: Three meetings a year, occurring from September to May.

North Pacific Pediatric Society

President: Dr. Percy Guy, 502–2d Ave., Seattle, Wash.
Secretary: Dr. Aldis B. Johnson, 515 Cobb Bldg., Seattle, Wash.

Northwestern Pediatric Society

President: Dr. George Kimmel, Redwing, Minn.
Secretary-Treasurer: Dr. Northrop Beach, 1009 Nicollet Ave., Minneapolis.
Place: Minneapolis, St. Paul, Duluth and Rochester. Time: January, April, July and October.

Rocky Mountain Pediatric Society

President: Dr. Jackson L. Sadler, 109 W. Olive St., Ft. Collins, Colo.
Secretary: Dr. Edwin T. Williams, 1850 Gilpin St., Denver 6.

Southern Medical Association, Section of Pediatrics

Chairman: Dr. Stewart H. Welch, 117 S. 20th St., Birmingham 5, Ala.
Secretary: Dr. W. Ambrose McGee, 1601 Monument Ave., Richmond 20, Va.

STATE

Alabama Pediatric Society

President: Dr. Jerome C. Chapman, 2160 Highland Ave., Birmingham.
Secretary-Treasurer: Dr. Ruth Berrey, 2021–6th Ave. N., Birmingham.

Arizona Pediatric Society

President: Dr. W. P. Sherrill, 342 W. McDowell Rd., Phoenix.
Secretary: Dr. W. F. Schoffman, 926 E. McDowell Rd., Phoenix.
Place: Phoenix or Tucson. Time: At time of state meeting.

Arkansas State Pediatric Association

Chairman: Dr. C. B. Billingsley, 1425 N. 11th St., Fort Smith.
Secretary: Dr. R. E. Weddington, 1425 N. 11th St., Fort Smith.

California State Medical Society, Section on Pediatrics

Chairman: Dr. Charles W. Leach, 2000 Van Ness Ave., San Francisco 9.
Secretary: Dr. Chester I. Mead, 1930 Truxton Ave., Bakersfield.

Florida State Pediatric Society

President: Dr. James R. Boulware, Lakeland.
Secretary: Dr. Hugh A. Carithers, 2000 Park St., Jacksonville 4.
Place: Concurrent with state association convention and fall meeting.

Georgia Pediatric Society

President: Dr. Alton Johnson, 102 E. Central Ave., Valdosta.
Secretary-Treasurer: Dr. Don F. Cathcart, 478 Peachtree St. N. E., Atlanta.
Place: Atlanta. Time: At time of annual state meeting.

Hezekiah Beardsley Pediatric Club of Connecticut

President: Dr. David Gaberman, 1179 Allyn St., Hartford, Conn.
Secretary: Dr. Herman Yannet, Southbury Training School, Southbury.

Illinois State Medical Society, Section on Pediatrics

Chairman: Dr. Gerard N. Krost, 2376 E. 71st St., Chicago.
Secretary: Dr. Frederick H. Maurer, 331 Fulton St., Peoria 2.

Indiana State Pediatric Society

President: Dr. K. T. Knode, 1105 E. Jefferson Bldg., South Bend.
Secretary-Treasurer: Dr. Matthew Winters, 621 Hume Mansur Bldg., Indianapolis.
Time: Two meetings a year.

Iowa Pediatric Society

President: Dr. Arnold M. Smythe, 406–6th Ave., Des Moines.
Secretary-Treasurer: Dr. James Dunn, 414 Blackhawk Hotel, Davenport.

Louisiana State Pediatric Society

President: Dr. S. George Wolfe, 1560 Line Ave., Shreveport.
Secretary-Treasurer: Dr. W. C. Rivenbark, 1448 Louisiana Ave., New Orleans 15.

Medical Society of State of New York, Section on Pediatrics

Chairman: Dr. Carl H. Laws, 12 Pierrepont St., Brooklyn, N. Y.
Secretary: Dr. George R. Murphy, 292 Madison Ave., New York.

Medical Society of the State of Pennsylvania, Pediatric Section

Chairman: Dr. Joseph A. Gilmartin, 3700–5th Ave., Pittsburgh 13.
Secretary: Dr. Carl C. Fischer, 100 W. Coulter St., Philadelphia 44.

Michigan State Medical Society, Pediatric Section

Chairman: Dr. Donald J. Barnes, 3001 W. Grand Blvd., Detroit, Mich.
Secretary: Dr. Mark F. Osterlin, Central Michigan Children's Clinic, Traverse City.

Mississippi State Pediatric Society

President: Dr. Harvey F. Garrison Jr., 315 E. Capitol Pl., Jackson.
Secretary: Dr. Guy Verner, 126 N. Congress St., Jackson.

Nebraska Pediatric Society

President: Dr. Paul N. Morrow, 1614 Medical Arts Bldg., Omaha 2.
Secretary-Treasurer: Dr. Michael Crofoot, 1407 Medical Arts Bldg., Omaha 2.
Place: As announced by committee. Time: Third Thursday of each month from October to June, inclusive. Dinner at 6 p. m.

New Mexico State Pediatric Society

President: Dr. M. K. Wylder, 221 W. Central Ave., Albuquerque.
Secretary-Treasurer: Dr. Ly Werner, 221 W. Central Ave., Albuquerque.

North Carolina Pediatric Society

President: Dr. Charles R. Bugg, Professional Bldg., Raleigh.
Secretary: Dr. Charles F. Williams, 817 Hillsboro St., Raleigh.

Northern California Pediatric Society

President: Dr. Edith M. Meyers, 431–30th St., Oakland.
Secretary: Dr. A. L. Gleason, 411–29th St., Oakland 9.
Place: San Francisco. Time: Second Thursday of February, April, September and November.

Oklahoma State Pediatric Society

President: Dr. J. B. Snow, 625 N. W. 10th St., Oklahoma City.
Secretary: Dr. Bertha Levy, 1200 N. Walker St., Oklahoma City.
Place: With Oklahoma State Medical Association. Time: Annual Meeting.

South Carolina Pediatric Society

President: Dr. George D. Johnson, Spartanburg.
Secretary-Treasurer: Dr. B. O. Ravenel. Roper Hospital, Charleston.

Tennessee Pediatric Society

President: Dr. F. T. Mitchell, 376 S. Bellview, Memphis.
Secretary-Treasurer: Dr. W. O. Vaughan, 2103 Hayes St., Nashville 5.
Time: Second Monday in April.

Texas Pediatric Society

President: Dr. Max Woodward, 202 N. Travis St., Sherman.
Secretary-Treasurer: Dr. John E. Ashby, 3610 Fairmount Ave., Dallas 4.

Virginia Pediatric Society

President: Dr. Emily Gardner, 1100 W. Franklin St., Richmond 20.
Secretary: Dr. Louise Galvin, 214 S. Boulevard, Richmond 21.

West Virginia State Medical Society, Section on Pediatrics

President: Dr. Jack Basman, 1021 Quarrier St., Charleston.
Secretary: Dr. Harry E. Baldock, Medical Arts Bldg., Charleston.

LOCAL

Academy of Medicine of Cleveland, Pediatric Section

Chairman: Dr. J. I. Hartman, 10515 Carnegie Ave., Cleveland.
Secretary: Dr. Alexander N. Freed, 2012 W. 25th St., Cleveland.
Place: Cleveland Medical Library Bldg. Time: 8:15 p. m., October, December, February and April.

Academy of Medicine, Toronto, Section of Pediatrics

President: Dr. J. H. Ebbs, 13 Queen's Park, Toronto, Canada.
Secretary: Dr. J. F. McCreary, 170 St. George St., Toronto, Canada.
Place: Academy of Medicine. Time: 8:30 p. m., third Thursday of each month.

Baltimore City Medical Society, Pediatric Section

Chairman: Dr. Charles O'Donovan Jr., 5 E. Read St., Baltimore.
Secretary: Dr. T. Campbell Goodwin, 16 E. Biddle St., Baltimore.

Bronx Pediatric Society

President: Dr. Harry S. Pizer, 1726 Davidson Ave., New York.
Secretary: Dr. Nathan M. Greenstein, 1488 Metropolitan Ave., New York.
Place: Morrisania City Hospital. Time: 8:30 p. m., second Wednesday of each month, except June, July, August and September.

Brooklyn Academy of Pediatrics

President: Dr. George E. Brockway Jr., 176 Fenimore St., Brooklyn.
Secretary: Dr. Bernard Benjamin, 845 Park Pl., Brooklyn 16.
Place: Granada Hotel. Time: 8:45 p. m., fourth Wednesday of February, March, April, October and November.

Buffalo Pediatric Society

President: Dr. Douglas P. Arnold, 159 Bidwell Parkway, Buffalo, N. Y.
Secretary: Dr. Richard A. Downey, 786 Forest Ave., Buffalo 9, N. Y.
Place: Children's Hospital, 219 Bryant St. Time: 8:30 p. m., first Monday of each month from September to June.

Central New York Pediatric Club

President: Dr. Arthur W. Benson, 2 St. Paul St., Troy.
Secretary: Dr. Frank J. Williams, 58 S. Swan St., Albany.
Places: Various cities in New York. Time: Third Tuesday of April and October.

Chicago Pediatric Society

President: Dr. H. William Elghammer, 2371 E. 71st St., Chicago.
Secretary: Dr. Alvah L. Newcomb, 723 Elm St., Winnetka, Ill.
Place: Children's Memorial Hospital, 710 Fullerton Ave. Time: Third Tuesday of each month, October to May inclusive.

Cincinnati Pediatric Society

President: Dr. Leo S. Friedman, 666 Rockdale Ave., Cincinnati 29.
Secretary: Dr. George Renner, 3144 Jefferson Ave., Cincinnati.
Place: Children's Hospital, Elland Ave., Cincinnati. Time: On call.

Dallas Pediatric Society

President: Dr. Shirley Hodges, 2703 Oak Lawn Ave., Dallas, Texas.
Secretary-Treasurer: Frances M. Love, 4585 Belfort, Dallas 4.
Place: Children's Medical Center. Time: 1 p. m., third Saturday and 8:30 p. m., the first Thursday of each month.

Detroit Pediatric Society

President: Dr. Otto Grob, 651 Fisher Bldg., Detroit 2, Mich.
Secretary: Dr. Harold B. Rothbart, 773 Fisher Bldg., Detroit 2, Mich.
Place: Variable. Time: Third Wednesday of each month.

Houston Pediatric Society

President: Dr. George Salmon, 1220 Bartlett St., Houston, Texas.
Secretary: Dr. Betty Moody, 526 Richmond Rd., Houston, Texas.
Place: River Oaks Country Club. Time: 7:30 p. m., last Tuesday of each month

Kansas City (Missouri) Pediatric Society

President: Dr. Harry M. Gilkey, 1624 Professional Bldg., Kansas City.
Secretary: Dr. Leland Speer, 1022 Parkway, Kansas City.
Place: Kansas City General Hospital. Time: On call.

Knoxville-Oak Ridge Pediatric Society

President: Dr. Henry S. Christian, 205 Medical Arts Bldg., Knoxville, Tenn.
Secretary: Dr. John Eggleston, Oak Ridge Hospital, Oak Ridge, Tenn.

Los Angeles County Medical Association, Pediatric Section

President: Dr. Elena Boder, 1830½ Lucille Ave., Los Angeles 26.
Secretary-Treasurer: Dr. Robert Simonds, 267 S. Beverly Dr., Beverly Hills, Calif.
Place: Los Angeles County Medical Association Bldg., 1925 Wilshire Blvd. Time: Second Monday of February, April, June, October and December.

Medical Society of the County of Kings and the Academy of Medicine of Brooklyn, Pediatric Section

President: Dr. Henry Rascoff, 895 Eastern Parkway, Brooklyn.
Secretary: Dr. Harold Levy, 750 St. Marks Ave., Brooklyn.
Place: 1313 Bedford Ave., Brooklyn. Time: 9:00 p. m., fourth Monday of each month.

MEDICAL SOCIETY OF THE COUNTY OF QUEENS, INC., SECTION ON PEDIATRICS

Chairman: Dr. Meyeron Coe, 217-02-91st Ave., Queens Village, N. Y.
Secretary-Treasurer: Dr. Louis Appel, 143-42 Cherry Ave., Flushing, N. Y.
Place: Queens County Medical Bldg., Forest Hills, N. Y. Time: Third Monday of October, January, March and May.

MEDICAL SOCIETY OF THE DISTRICT OF COLUMBIA, SECTION ON PEDIATRICS

President: Dr. John Washington, 2203 Wyoming Ave., Washington, D. C.
Secretary-Treasurer: Dr. George Maksim, 1418 Good Hope Rd. S.E., Washington, D. C.
Place: Medical Society Bldg., 1718 M St. N. W. Time: 8 p. m., third Thursday of October, January, March and May.

MEMPHIS PEDIATRIC SOCIETY

President: Dr. Kinsey M. Buck, 1193 Madison Ave., Memphis, Tenn.
Secretary-Treasurer: Dr. Barton Etter, 1024 Madison Ave., Memphis, Tenn.

MILWAUKEE PEDIATRIC SOCIETY

President: Dr. G. H. Fellman, 231 W. Wisconsin Ave., Milwaukee.
Secretary-Treasurer: Dr. R. P. Showalter, 411 E. Mason St., Milwaukee 2.
Place: Milwaukee Children's Hospital. Time: Second Wednesday in February, April, June, October and December.

NEW YORK ACADEMY OF MEDICINE, SECTION OF PEDIATRICS

Chairman: Dr. Robert O. Du Bois, 122 E. 76th St., New York.
Secretary: Dr. Harold W. Dargeon, 1095 Park Ave., New York.
Place: New York Academy of Medicine, 2 E. 103d St. Time: Second Thursday of each month from November to May, inclusive, 8:30 p. m.

OKLAHOMA CITY PEDIATRIC SOCIETY

President: Dr. J. B. Snow, 625½ N. W. 10th St., Oklahoma City.
Secretary: Dr. Bertha Levy, 1200 N. Walker St., Oklahoma City.
Place: Oklahoma Club. Time: Third Thursday of each month.

PHILADELPHIA PEDIATRIC SOCIETY

President: Dr. Arthur M. Dannenburg, 235 S. 15th St., Philadelphia 2.
Secretary: Dr. D. Stewart Polk, Rosemont, Pa.
Place: College of Physicians, 19 S. 22d St. Time: 8:30 p. m., second Tuesday from October to May, inclusive.

PITTSBURGH PEDIATRIC SOCIETY

President: Dr. Elwood Stitzel, 403 Central Trust Bldg., Altoona, Pa.
Secretary-Treasurer: Dr. C. J. Stoecklein, Medical Arts Bldg., Pittsburgh 13.
Place: Pittsburgh Academy of Medicine. Time: Second Friday in October, December, February and April.

RICHMOND PEDIATRIC SOCIETY

President: Dr. Edwin L. Kendig Jr., 828 W. Franklin St., Richmond 20, Va.
Secretary-Treasurer: Dr. Thomas S. Chalkley, 1200 E. Broad St., Richmond, Va.
Place: Medical College Hospital. Time: 8 p. m., third Thursday of each month, except June, July and August.

SEP 23 1947

Rochester Pediatric Society

President: Dr. Jerome Glaser, 300 S. Goodman St., Rochester 7, N. Y.
Secretary-Treasurer: Dr. Daniel B. Peeler, 1162 Lake Ave., Rochester 13, N. Y.
Place: Rochester Academy of Medicine or arrangement by program committee.
Time: Third Friday of each month from October to May.

St. Louis Pediatric Society

President: Dr. Joseph C. Jaudon, 337 N. Euclid Ave., St. Louis.
Secretary-Treasurer: Dr. Gilbert B. Forbes, 500 S. Kingshighway, St. Louis 10.
Time: Second Thursday of each month from October to May, inclusive.

San Antonio Pediatric Society

President: Dr. Sidney R. Kaliski, 518 Moore Bldg., San Antonio 5.
Secretary-Treasurer: Dr. Edith M. Bonnet, 228 Medical Arts Bldg., San Antonio 5.
Place: Variable. Time: 7:30 p. m., first Tuesday of every month.

Seattle Pediatric Society

President: Dr. Norman W. Murphy, 1300 Madison St., Seattle 4.
Secretary: Dr. David M. Harris, 630 Medical Arts Bldg., Seattle 1.
Place: College Club. Time: Third Friday of each month from September to June at 6:30 p. m.

Southwestern Pediatric Society

President: Dr. Donald C. Shelby, 416 N. Bedford Dr., Beverly Hills, Calif.
Secretary: Dr. Harry F. Dietrich, 416 N. Bedford Dr., Beverly Hills, Calif.
Place: University Club of Los Angeles. Time: 6:30 p. m., first Wednesday in January, March, May, September and November.

University of Michigan Pediatric and Infectious Disease Society

President: Dr. Park Bradshaw, Muskegon, Mich.
Secretary: Dr. Harry A. Towsley, 1313 E. Ann St., Ann Arbor, Mich.

Westchester County Medical Society, Pediatrics Section (New York)

President: Dr. John B. Ahouse, 27 Ludlow St., Yonkers, N. Y.
Secretary-Treasurer: Dr. Elvira Ostlund, 64 Highland Rd., Rye, N. Y.
Place: Hospitals of Westchester County. Time: Third Thursday in November, January, March and May.